Atherosclerotic Lesions in Diabetes

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Since arteriosclerosis accounted for 69.4 per cent of deaths in a series of diabetic subjects in the five-year period from 1944 to 1949,[1] it seems appropriate to reassess our knowledge of this serious complication of diabetes in the last trimester of 1954.

"Atherosclerotic lesions" I have interpreted as meaning those lesions, primarily intimal, which occur in the large and medium-size arteries of the body. Within the limitations of this paper the term "atherosclerosis" will be considered to be synonymous with arteriosclerosis of the intimal type. I propose to discuss atherosclerosis from the pathologist's point of view, to consider the relationship between this disease and diabetes, and to summarize some of the problems that confront investigators in the field of arteriosclerosis.

DEVELOPMENT OF THE LESION

Almost all pathologists are of the opinion that the earliest visible lesions of atherosclerosis are the minute, slightly elevated yellow flecks seen in the aortas of children. Holman and Strong[2] in a series of 120 patients ranging from one to seventeen years of age found no child over the age of three years who was exempt from these lesions; Zinserling[3] saw them in 95.4 per cent of 302 children under sixteen years. The flecks tend to coalesce, forming longitudinal streaks along the long axis of the posterior wall of the aorta and small elevations at the orifices of the intercostal arteries. Although the disease involves the thoracic portion of the aorta predominantly before the age of twenty, the lesions encountered in children up to six years are more abundant in the ascending portion of the arch.[3] After the age of twenty the abdominal aorta is the most severely involved area. Thus it appears that the lesions progress distally in the aorta, increasing in size, severity, and incidence.

The fatty flecks and streaks in the aortas of children are not limited to the juvenile type of atherosclerosis but represent the fundamental pattern of atherosclerosis seen in the lesions of adults. The development of lesions in other arteries is identical, although the structure of the wall of those arteries differs in the thickness of the intima and the composition of the media.

On anatomic grounds there is presumptive evidence that the lipid in the lesions is not static.[4] The flecks and streaks may regress to a point where they are no longer visible, or they may remain as fibrotic areas devoid of sudanophilic material. In the majority, however, lipid continues to accumulate and is covered by connective tissue. The thickness of this covering determines the appearance of the plaque, which may vary from bright yellow to pearly gray. It is unusual to observe these so-called pearly plaques before the age of thirty-five. Lipid in the central portions of the lesion undergoes necrosis and forms the "mush" from which the name atheroma is derived. From this stage the lesion may enlarge until it coalesces with neighboring plaques, or the thickened intima may become so distended that it ruptures and the grumous material is then discharged into the blood stream, leaving behind an ulcerated surface to which thrombi become attached. The plaque may also destroy the underlying muscle and elastic tissue so that the wall is weakened and dilatation occurs.

Microscopic examination of the juvenile lesions shows a swelling of the ground substance of the intima with metachromasia and minute lipid droplets scattered throughout it. These droplets are predominantly in the deeper layers of the intima and are rarely intracellular. Later foam cells laden with fat and mesenchymal cells accumulate. As the fibrous tissue proliferates the foam cells are compressed, and many disintegrate, leaving a collection of debris in which pyknotic nuclei, cholesterol crystals, and large amounts of sudanophilic material can be identified. Foam cells and a few lymphocytes are seen at the margins of the lesion. Changes are not confined to the intima, even in the early lesions, for there is abundant lipid present in the upper layers of the media and along the elastic lamellae. This is present even though the elastic membrane remains intact, but it would appear that the elastica does act as a more or

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less effective barrier against the accumulation of lipid in the media.

As the lesion progresses, it exhibits the pleomorphism which is well-known. The thickened fibrous tissue may undergo hyalinization, still retaining droplets of lipid, or it may ulcerate. Hemorrhage may occur in the plaques due to the rupture of newly formed or pre-existing vasa vasorum. Calcium may be precipitated; the elastic tissue becomes frayed and reduplicated. As lipid penetrates the media, the muscle cells atrophy and become separated. The adventitia, as though to strengthen the damaged wall, acquires additional layers of fibrous tissue, which may become hyalinized.

Turning from this description of the lesion to arteries other than the aorta, the pathologist can trace a basic pattern of evolution of the disease. The coronary arteries develop similar lesions, but usually later than the aorta. They occur only as small macroscopic flecks or streaks in the first decade. Holman[5] states that he has never seen an arteriosclerotic lesion of the coronary in a child in the absence of an aortic lesion. However, in young adults it is not uncommon to observe a severe segmental sclerosis of the coronary arteries with minimal involvement of the aorta. The coronary plaques are usually situated near the origins of the vessel and extend peripherally toward the small epicardial branches, but are seldom seen in the branches penetrating and covered by the myocardium. The entire histopathologic sequence described above may occur within the coronary plaque. Paterson[6] has emphasized that these lesions tend to vascularize and to be subject to hemorrhage and formation of hematomas. Because of hemorrhage the lumen may be narrowed or the plaque may rupture, thus setting the stage for thrombosis. Various observations[7, 8] on the structure of the coronary arteries in male versus female infants have led some investigators to conclude that the irregular thickening of the intima, which is greater in males, accounts for the increased incidence of coronary disease therein. The high incidence of cardiac infarction in female diabetic subjects casts serious doubt on this concept.

The cerebral arteries develop plaques much later than the coronaries or the aortas. It is rare to find plaques in an individual younger than thirty. The lesions are identical with those seen elsewhere, but Duff[4] has called attention to a peculiarity of the cerebral arteries, where at the point of interruption of the internal elastica lipid can be seen pouring through the gap and destroying the media. A series of post-mortem examinations of 866 diabetic individuals in whom arteriosclerosis was considered the major cause of death revealed that cerebral arteriosclerosis was the lethal factor in only 9.7 per cent.[1] It is noteworthy that the incidence is no greater than in nondiabetics.

The intimal plaques that develop in the arteries of the extremities are predominantly fibrous at the time they are examined, but lesions rich in lipid and identical with those found in other arteries are not unusual. Warren[9] has commented on the frequency of the lipid-rich lesions in the peripheral arteries of diabetic subjects. In the series quoted above, the incidence of death due to gangrene of the lower extremities was 9.4 per cent. This was one-fourth the incidence of an earlier series and probably reflects the influence of antibiotic therapy as well as of education of the diabetic in the care of his feet.[1]

RELATION OF ATHEROSCLEROSIS TO DIABETES

Despite the morphologic identity of the atheromatous lesions in diabetics and in nondiabetics, there are certain variations of the lesion in diabetics. The abundance of lipid in the plaques in the peripheral arteries has been mentioned. Lipid-rich atheromatous lesions often occur in the renal arteries of patients with the Kimmelsteil-Wilson syndrome, whereas they occur rarely in the renal arteries of nondiabetics with other forms of chronic renal disease.

Almost no one will dispute the statement that diabetes accelerates the development of arteriosclerosis. The experience of pathologists who can cite post-mortem examinations of aged patients with diabetes of long standing in which less arteriosclerosis is seen than in nondiabetic subjects indicates that diabetes cannot be a cause of arteriosclerosis. Indeed, in Warren and LeCompte's[1] series of 816 autopsies of diabetics 66 were described as free of aortic atheromata. The absence of aortic lesions might be questioned, but the statement implies that the lesions were not conspicuous and hence probably less than the number expected. This small group of diabetics who enjoy relative freedom from atherosclerosis warrants intensive study.

Is good control of diabetes in these individuals responsible for their relative freedom from arteriosclerosis? Evidence both for and against this has been submitted. Wilson, Root, and Marble[10] found less *clinical* evidence of vascular disease in young diabetics of long duration under the authors' standards of excellent or good control than those under fair or poor control. In contrast, Bell[11] concluded from post-mortem studies that severe vascular lesions are independent of the severity of the diabetes, although he believed that the severity of the lesions increased with the duration of the diabetes in patients

who died before the age of sixty. Much more accurate data regarding this should be forthcoming with the terminal study of the Quarter-Century Victory Medal diabetics reported by Joslin.[12]

Do cases of diabetes differ in some subtle and as yet undetected way? We can only speculate on this. To assume that the knowledge obtained from experiments on diabetic animals can be applied to human beings is hazardous. Duff and others[13–15] have demonstrated that the development of atheromatous lesions of the aorta in cholesterol-fed rabbits was retarded in animals with alloxan diabetes. If the diabetes of these animals was treated with insulin the inhibitory effect was abolished and the lesions were similar to the nondiabetic cholesterol-fed controls. Similarly the majority of investigators of the cortisone-induced diabetes of rabbits report significantly less lipid deposition in the aorta, despite large increases in blood lipid fractions in the cholesterol-fed rabbits treated with cortisone in contrast to the nondiabetic cholesterol-fed controls.[16–18]

Little investigation of diabetes and atherosclerosis has been done in other species. Allen and Lisa[19] found no vascular lesions in a dog made diabetic for twelve years by partial pancreatectomy and with the diabetes controlled by diet and insulin. Dragstedt,[20] on the other hand, reports an increased incidence of arteriosclerosis in a series of 160 depancreatized dogs (15 per cent against 2 per cent in 400 controls). These observations were made on dogs of unknown age obtained from the pound.

If arteriosclerosis is due, at least in part, to a defect in lipid metabolism or lipid transport, it is entirely possible that the disturbance of carbohydrate metabolism in the diabetic contributes to this. Until comparatively recent years little has been known of lipid transport. The report of Barr[21] on the percentage of alpha and beta lipoprotein in diabetics four to thirty-five years of age is of great interest, for it is evident that their lipid pattern is almost identical with that of persons who have survived myocardial infarction and approaches that in rabbits and dogs rendered arteriosclerotic.

A rare disease of great interest is progeria and its variations, which masquerade under such names as Werner's syndrome in the adult and Rothmund's or Hutchinson-Gilford's syndromes in children. Advanced sclerosis of the arteries often leads to the death of children so afflicted before the age of ten. Diabetes is a common occurrence in this group of diseases.[22–24]

In view of the recent work of Friedenwald[25] and the correlation of the microaneurysms of the retina and glomerular capillary lesions in diabetic subjects, one cannot ignore the role that the capillary bed may play in accentuating the atherosclerotic lesions of the large arteries of diabetic subjects.

PROBLEMS IN ARTERIOSCLEROSIS

Ignorance of the pathogenesis of arteriosclerosis has resulted in a succession of theories, to be championed and discarded as their inadequacy became manifest. Current concepts tend to implicate a chemical or physiochemical disturbance of lipid metabolism, but the more recent papers also acknowledge the importance of the arterial wall. This fact is consoling to many pathologists who were beginning to suspect that arteriosclerosis was an "in vitro" disease.

Foremost among the difficulties of investigation is the fact that arteriosclerosis is a qualitative as well as a quantitative disease. One plaque strategically placed in a coronary artery can be fatal, yet individuals with hundreds of plaques in practically every artery, with aneurysms, with thrombi loosely attached to ulcerated surfaces, and with even complete occlusion of an artery may not only enjoy long life but remain asymptomatic. Secondly, arteriosclerosis is an almost universal disease in man, beginning early in life and continuing in episodic fashion until death. Because of these two facts the value of chemical tests designed to detect atherosclerosis or to measure its severity can be questioned.

EVALUATION OF PRESENT KNOWLEDGE

It is generally agreed that atherosclerosis begins early and progresses with age, although it is not necessarily associated with aging. The localization of atheromatous deposits about sites of injury and in particular areas in normal blood vessels and the acceleration of the disease in hypertension support the opinion that anatomic variation and hemodynamics play an important role.

The coexistence of early and advanced lesions in close proximity implies that the causative agent acts discontinuously, and offers some hope that it might be interrupted.

The predominantly lipid nature of the atheromatous material has led to the opinion that the vessel wall acts as a more or less selective filter, capable of holding back certain lipid fractions. Wilens,[26] who has filtered plasma with varying lipid content through excised human iliac arteries, has established that at least in vitro the arterial wall can retain certain fractions of plasma lipids as measured by chemical analysis and microscopic examination. Others have maintained that the vessel wall

disposes of lipids under normal conditions.

The precocious development of arteriosclerosis in diseases associated with abnormal lipid patterns, such as diabetes, nephrosis, myxedema, and familial xanthomatosis, has formed the foundation for the vast experimental work in animals.

By altering the lipid patterns appropriately in various animal species such as the rabbit, chicken, dog, and recently monkeys, lesions resembling those of human disease can be produced. Arguments have been waged as to whether this disease is comparable to that in man, since development of the human lesion is apparently not dependent on such severe abnormalities of plasma lipids. Nevertheless, the production of the disease or at least a facsimile of it has offered the one useful approach toward an understanding of its pathogenesis. By observing the behavior of the lesions when the animal is taken off a regimen which entails the feeding of cholesterol-rich diets and is kept on normal stock diet for varying lengths of time, one can trace the pathways of removal of atheromatous material and the attempts at repair of the vessel wall. That an analogous situation exists in man is suggested by observations on human autopsy material where the lesions of those who were undernourished or who had lost considerable weight rapidly seemed to contain much less lipid than those who had not lost weight prior to death.[27]

The relation of obesity to arteriosclerosis has been emphasized.[28, 29] There seems little doubt that the presence or severity of arteriosclerosis is correlated with a state of good nutrition or overnutrition. Contrariwise, populations on low-fat diets seem to gain a measure of protection against the consequences of arteriosclerosis.[30]

We have limited knowledge of the influence of the endocrine factors on arteriosclerosis. For example, we know that it is impossible to produce arteriosclerosis in the dog by cholesterol feeding without depressing thyroid function either by thyroidectomy or the use of thiouracil.[31] Turner[32] and Katz[33] have prevented or suppressed the development of arteriosclerosis in rabbits and chicks by giving desiccated thyroid. Conflicting results have been obtained with the use of inorganic iodides.[34] Dinitrophenol, a drug which increases metabolism, is without influence on the production of lesions in the chick, suggesting that the action of thyroid is not simply a function of increased metabolism.[35] The administration of desiccated thyroid to dogs after withdrawal of the atherogenic regimen had no influence on the rate of regression of the lesions.[36]

One of the vagaries of arteriosclerosis that has been of great concern is the disparity in incidence of fatal coronary disease between the sexes. This lessens rather abruptly after the female menopause, until between fifty-five and sixty the ratio becomes almost equal. Thus attention has been focused on the possible role of estrogenic substances on the pathogenesis of arteriosclerosis. We have been unable to influence the rate of regression of atherosclerotic lesions in dogs by the administration of an estrogen orally.[36] However, Katz[34] and his co-workers report that in cockerels the administration of estradiol both prophylactically and therapeutically has selectively inhibited or prevented lesions in the coronary arteries but not in the aorta. Barr[21] and the Goldwater group[37] have given estrogens to males surviving myocardial infarction and have noted shifts in the lipid patterns toward so-called normalcy but have not noted clinical improvement in the anginal syndrome. Testosterone has exaggerated the abnormalities in the lipid pattern.

The influence of pancreatectomy in dogs has been touched on, and results by different investigators using various diets have been equivocal.[20] Alloxan diabetes and cortisone-induced hyperglycemia have prevented or inhibited lesions in cholesterol-fed rabbits. In contradiction there is a report of precocious atherosclerosis in children treated with cortisone.[38]

We still have insufficient knowledge of the enzyme systems necessary for the metabolism of lipid protein or carbohydrates, much less their intercepting pathways. Of interest are the recent investigations of the Harvard group,[39] who have succeeded in producing atherosclerotic lesions in methionine-deficient cholesterol-fed monkeys and have prevented their appearance by the addition of methionine to the diet.

Within the circumscribed field of the morphologist, restricted as it is by visual observation, there is a surprising lack of agreement. Interpretations of the nature and significance of the structural changes of atherosclerosis have differed widely. Duff and Leary[4] have long championed the importance of metabolism at the cellular level, especially the metabolism of lipids in the arterial intima. It is only when we know what goes on within the cell itself and its immediate environment that we can settle the argument as to whether increased or decreased permeability of the intima, or defense mechanisms inherent in the unaffected portion of the arteries operate to prevent the formation of lesions. Recent studies on the synthesis of cholesterol in arterial walls are contributing to our understanding of cellular metabolism. Further elucidation should come from studies of the ground substance of the intima, whose metachromasia and swelling are at present our earliest indication of the developing lesion.

SUMMARY

There is general agreement regarding the following observations: (1) Atherosclerosis begins early, progresses with age, and localizes in particular sites, especially in relation to injury and stress. (2) It is characterized by deposition of lipid material in the blood vessel wall. (3) The vascular change is accelerated by diseases in which there is disturbance of lipid metabolism.

There appears to be evidence that: (1) Atherosclerosis can be produced in animals by altering lipid patterns. (2) It is capable of regressions. (3) It is associated with good nutrition in man.

There is need for more knowledge of (1) the influence of endocrine products and specific enzymes, and (2) the metabolism of lipids at the cellular level.

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DISCUSSION

AARON KELLNER, M.D., (*New York*): Dr. Bevans has summarized in an exceedingly able and concise fashion our present knowledge, or lack of knowledge, of atherosclerosis. I was particularly pleased at the emphasis that Dr. Bevans placed upon morphology. The pendulum, as you well know, has swung away from morphology in recent years, and it is distinctly out of style to be a morphologist today. Yet, much remains to be learned by carefully thought out and well-directed morphological studies. This is particularly true of atherosclerosis which, despite the advances that have been made in our knowledge of lipid metabolism and lipid transport, is still defined in morphological terms. As a matter of fact, we are not even sure whether what we so define in morphological terms is one disease or a group of diseases.

Dr. Bevans emphasized quite correctly the importance of the very early lesions in atherosclerosis, what pathologists refer to descriptively as metachromasia and swelling of ground substance. It is here that morphological studies need particularly to be focused, making use of the newer optical and histochemical technics, because at the present time we do not know what the very early stages of this disease are, and we are not even certain whether lipids are in fact the primary offending agents, as many of us think, or whether, as others think, they are secondary phenomena.

Our experience at the New York Hospital with diabetes and atherosclerosis has been similar to that of Dr. Bevans and most others. It is our feeling that diabetics have considerably more atherosclerosis as a group than do nondiabetics of comparable age, and we, too, have been impressed by the fact that although females under the age of forty-five have a remarkable relative immunity to atherosclerosis, this immunity is abolished by diabetes or by hypertension.

Despite the fact that atherosclerosis seems to be more severe, more common, and to occur at an earlier age in diabetics, we are every now and again surprised to see a diabetic well on in years who has had diabetes for twenty or thirty years, who comes to post-mortem examination and is singularly free of atherosclerosis. This is a natural experiment which bears careful consideration. It may be that diabetes is a different disease in some individuals than in others. Perhaps not all diabetes is at its root the same disease.

Finally, I should like to ask Dr. Bevans whether she has had an opportunity to study the anatomical changes in the lower extremities of diabetics. Bell, in a study some four or five years ago, found that occlusive vascular disease of the lower extremities was forty times as common in diabetics as in nondiabetics. If this is due entirely to atherosclerosis, there must be something unique about the vessels of the lower extremities, because the coronary arteries of diabetics are not forty times as vulnerable to atherosclerosis. Diabetics do not have forty times as many myocardial infarctions nor forty times as many aneurysms of the aorta as nondiabetics. Is there something unique about the vessels of the lower extremities, perhaps some still undefined disease of the blood vessels, which occurs in diabetics and not in nondiabetics?

DR. BEVANS (*closing*): In answer to Dr. Kellner's question, I have had some experience in dissecting limbs of diabetics but not in recent years, however, when I might have been more interested than I once was. A rather intriguing thought occurred to me as I was writing this paper and that is that the cerebral lesions in diabetics are no more common than those in the nondiabetic population, but as we progress distally in the body, the lesions of the aorta seem to be more severe in diabetics, the lesions of the coronary arteries more severe, and so on down to the lower extremities where, as Dr. Kellner says, they are forty times as severe in diabetics. I think this warrants a little thought.

SUMMARIO IN INTERLINGUA

Lesiones Atherosclerotic in Diabete

Le sequente observationes es generálmente acceptate como ver: (1) Atherosclerosis comencia a bon tempore, progrede con le etate del patiente, e se localisa in sitos particular, specialmente in consequentia de vulnere o stress. (2) Atherosclerosis es characterisate per le deposition de materia lipide in le pariete del vaso de sanguine. (3) Le alteration vascular es accelerate per morbos in que le metabolismo lipide es disturbate.

Le sequente observationes es supportate per certe demonstrate datos: (1) Atherosclerosis pote esser producite in animales per alterar le balancia normal del lipidos. (2) Atherosclerosis pote passar per periodos de regression. (3) In homines atherosclerosis es associate con bon nutrition.

Le sequente problemas require studios additional: (1) Le influentia de productos endocrin e de specific enzymas. (2) Le metabolismo del lipidos in le cellula.

The Morphogeny of the Capillary Vascular Lesions of Diabetes

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Highly characteristic if not strictly specific alterations affect retinal and glomerular capillaries in patients with long-term diabetes. The morphologic characteristics of these lesions distinguish degenerative vascular disease in diabetic patients from that in nondiabetic individuals. Their presence differentiates the pattern of vascular degeneration in the retina and kidney from that so far demonstrated anatomically elsewhere in diabetic patients in whom these characteristic lesions occur. While there is disagreement among authorities, some regard the development of capillary lesions as an integral component and inevitable accompaniment of long-term diabetes, rather than as one of its complications.[1] Glomerular lesions are found in about 50 per cent of patients with retinal capillary involvement and are not present in patients without retinal lesions. Conversely, if they are looked for, retinal lesions are found in practically all patients with glomerular lesions.[2, 3] Thus there is a definite correlation between the incidence of retinal and renal involvement. The lesions do not appear to be strictly comparable morphologically. It has been suggested that they reflect similar pathologic processes, the manifestations of which are modified by structural differences between the capillaries concerned. It may also be that the interpretability of changes in the retina and glomerulus is concerned. The capillary network visualized in flat mounts of whole retinas has a rather simple pattern. In the glomerulus, about 2.5 cm. of capillaries branch and reanastomose within the confines of a sphere about 200 microns in diameter. Our concepts of the finer details of normal glomerular structure and its alterations in disease are changing with recent advances in microscopic and histochemical technics.

The current concept of the retinal lesion stems from the investigations of Ballantyne and Loewenstein,[4] of Ashton,[2] and of Friedenwald.[3] Together, these studies have shown that the pathologic anatomic counterpart of the punctate hemorrhage in diabetic retinopathy is a saccular capillary microaneurysm. These minute outpouchings of the capillary wall range in size from 20 to 100 microns. One important component of their walls is a hyaline substance which contains carbohydrate, and which in its tinctorial reactions with the periodic acid-Schiff stain resembles a component of normal capillary basement membranes. The basement membranes of capillaries which are free from aneurysms may be thickened by focal accumulations of hyaline, and the amount of periodic acid-Schiff positive material in the walls of aneurysms varies. Some have thin walls; others may be completely obliterated by hyaline deposits.

The characteristic glomerular lesion consists of clumps of periodic acid-Schiff positive hyaline material which appears to intervene between the lumens of capillaries. There have been differences of opinion regarding the origin and precise location of this material since Kimmelsteil and Wilson directed attention to the glomerular lesion in 1936.[5] From their observations, it was indicated that the hyaline originated and accumulated between intact capillary loops in mesangial tissue normally present. The intactness of the capillary basement membrane as a feature distinguishing this type of intercapillary glomerulosclerosis from that found in other hyalinizing glomerular diseases was stressed. Subsequently, A. C. Allen[6] and later Bell[7] concluded that the hyaline originated in the capillary wall, representing a distinctive type of sclerosis of the capillary, rather than a sclerosis of intercapillary connective tissue. These apparently opposing interpretations are not necessarily mutually exclusive. Evidence is accumulating which indicates that potential spaces normally present between glomerular capillaries, as well as around them, become filled with hyaline material.[8] The morphologic expression of the lesion, and the interpretation of its localization, may

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depend on which of these patterns predominates.

The essential feature of the characteristic diabetic glomerular alteration which allows its identification histologically is a focal clumping of hyaline material. As seen in a fully developed form, the distinctive Kimmelsteil-Wilson lesion is fairly well circumscribed and nodular, lying in the center of a glomerular lobule. Nodular lesions spare that side of the capillary wall on the outer surface of the loop; segmental hyalinization of the capillary wall does not. This axial distribution of nodular lesions is striking and constant and must have significance. It appears to reflect the existence of a potential axial space. Nodular lesions may be homogeneous, vacuolated, fibrillar, or lamellated. Concentric layers of compressed cells and irregular small focal deposits of hyaline material may be present, obscuring or obliterating the outlines of adjacent capillaries, or adjacent capillaries may appear quite normal. Sometimes overdistended capillary loops appear marginally. To some observers, these are analogous to the retinal capillary microaneurysms. However, this phenomenon can also be attributed to local mechanical obstruction. We have not found dilatation of capillaries to precede the stage of hyalinization, nor to occur in glomeruli which are free from large deposits of hyaline material. When large, the latter assume a rounded shape; smaller ones are irregular in contour. The hyaline deposits vary widely in size and number within a given glomerulus, and may involve a few glomeruli or almost all of them.

It is generally accepted that the nodular lesion is specific for diabetes. There are divergent opinions with regard to the so-called diffuse type of diabetic glomerulosclerosis,[9] not with regard to its occurrence but rather its definition, recognition, and specificity for diabetes. The anatomic features are simply not sufficiently distinctive to allow differentiation from similar alterations in nondiabetic patients. This in no way detracts from the functional significance of diffuse glomerulosclerosis, nor from its importance in a consideration of the evolution of the specific nodular lesion.

In about 50 per cent of patients with well-established capillary microaneurysms in the retina, the retinal arterioles are free from structural change.[8] On the other hand, in our experience and that of most other observers diabetic glomerulosclerosis is almost invariably associated with afferent arteriolar sclerosis. In fact, both afferent and efferent arteriolar sclerosis may be found, as pointed out by A. C. Allen,[6] a circumstance not hitherto described except in diabetes. It is of considerable interest that the staining reactions of the hyaline in arterioles are comparable to those of capillary basement membranes and of the hyaline deposits affecting them.

A link between the retinal and glomerular capillary lesions is the similarity of the staining reactions of the hyaline which accumulates in and around their walls. This material has an affinity for special stains for collagen,[6] frequently contains sudanophilic fat,[10] and is rich in carbohydrate.[11] Fahr[12] suggested that the formation of hyaline might be related to a local deposition of protein substances from the blood. Wilens, Elster and Baker[10] have proposed that the deposition of lipids might play a role in its development. McManus[13] speculated that polysaccharides circulating in abnormal amounts in the blood of diabetic patients might be the source of the hyaline material. In broad terms, these suggestions are reminiscent of the concept of a relationship between a disturbance of lipoprotein metabolism and atherosclerosis.

Normal human serum contains a relatively high concentration of complex polysaccharides bound to protein. The source, composition, and function of these glycoprotein substances are poorly understood. It has been demonstrated repeatedly that their concentration, and in some cases their composition, is altered in a variety of diseases.[14, 15] Some published observations, notably those of Jacobs, indicate that the concentration of polysaccharides, measured as glucosamine, is elevated in the serum of diabetic patients.[16] Other scattered figures suggest that diabetic patients have normal serum polysaccharide levels.[14, 15] The data in these studies are presented in such a way that the results obtained cannot be correlated with the absence or presence of vascular disease.

To explore the possibility of an association between a disturbance of polysaccharide metabolism and the occurrence of vascular disease in diabetic subjects, we have studied the serum polysaccharide levels in several groups of patients.[17, 18]

Group I consisted of 15 nondiabetic, nonarteriosclerotic controls.

Group II consisted of 78 patients with diabetes mellitus, further divided into three subgroups depending on a clinical evaluation of the presence and degree, or absence, of degenerative vascular disease, and evidence of the presence or absence of renal involvement.

Group II A included 26 diabetic patients *without* clinically detectable degenerative vascular disease.

Group II B included 18 diabetic patients with well-established manifestations of retinopathy, neuropathy, and occlusive coronary, cerebral or peripheral artery disease, in whom *proteinuria, hypertension, or renal*

msufficiency were absent.

Group II C included 34 diabetic patients, with varieties of vascular disease similar to those in II B, but who had in addition hypertension, proteinuria, or renal insufficiency. Fourteen of these patients had a full-blown Kimmelsteil-Wilson syndrome.[19] In 20 we could not ascertain whether renal involvement was by nephrosclerosis alone or by diabetic glomerulosclerosis as well.

Group III consisted of 14 nondiabetic patients with kidney disease. Of these, six had renal insufficiency on the basis of hypertensive renal vascular disease.

Group IV consisted of 30 nondiabetic patients with arteriosclerosis, some with hypertension, but none with evidence of impairment of renal function.

All patients included in this study were free from other diseases such as cancer, acute or chronic infections, and acute myocardial infarction which are known to be associated with elevations of serum polysaccharide levels.[14, 15]

Serum polysaccharides were measured both as galactose-mannose in the so-called total polysaccharide bound to serum protein[20] and as serum glucosamine.[14] From the data obtained (table 1, figure 1 and 2) it is evident that the concentrations of polysaccharides bound to serum protein and the concentration of serum glucosamine are significantly elevated in diabetic patients, not in association with the primary metabolic defect in diabetes mellitus, but only when well established clinically detectable degenerative vascular disease exists. Elevated levels are also found in nondiabetic patients with renal disease. However, increased concentrations are found in diabetic patients independent of the existence of abnormalities of renal function as evaluated by conventional clinical and laboratory methods. The levels in diabetic individuals with degenerative vascular disease are significantly higher than those in nondiabetic individuals with such complications. In a few nondiabetic patients with arteriosclerosis, the protein-bound polysaccharides are elevated to a degree comparable to that in the nondiabetic group, but in the majority of nondiabetics the values for total polysaccharides and for serum glucosamine are in the range of normal.

The degree of accuracy with which various stages and combinations of degenerative vascular lesions, or their severity, can be estimated clinically is of course far from reliable. However, it does seem reasonable to assume that the diabetic patients with vascular involvement had lesions of significantly greater extent and severity than did the nondiabetic patients with arteriosclerosis, and we do have some necropsy observations to bear this out.

Elevations of serum polysaccharides which have been produced experimentally and which occur spontaneously in disease are currently interpreted as a nonspecific response to tissue injury, and in particular to alterations of connective tissue polysaccharides. Changes in subintimal mucopolysaccharide ground substance have been implicated in the pathogenesis of arteriosclerosis, a local increase in subendothelial mucopolysaccharide being an early feature, preceding lipid deposition in the vessel wall.[21-23] It is quite possible that what we have found

TABLE 1

Serum concentrations of polysaccharide substances in the groups of patients studied

Group	No. of cases	Total polysaccharide bound to serum protein mg. per cent Mean ± S.D.	Glucosamine mg. per cent Mean ± S.D.
I. Nondiabetic controls	15	146 ± 11.2	97 ± 8.3
II. Diabetic			
A. Uncomplicated	26	143 ± 13.5	114 ± 8.6
B. Degenerative vascular disease without renal involvement	18	184 ± 21.5	145 ± 15.1
C. Degenerative vascular disease with renal involvement	34	193 ± 26.3	153 ± 20.2
III. Nondiabetic with renal disease	14	216 ± 47.5	148 ± 26.9
IV. Nondiabetic with degenerative vascular disease	30	147 ± 19.1	102 ± 11.8

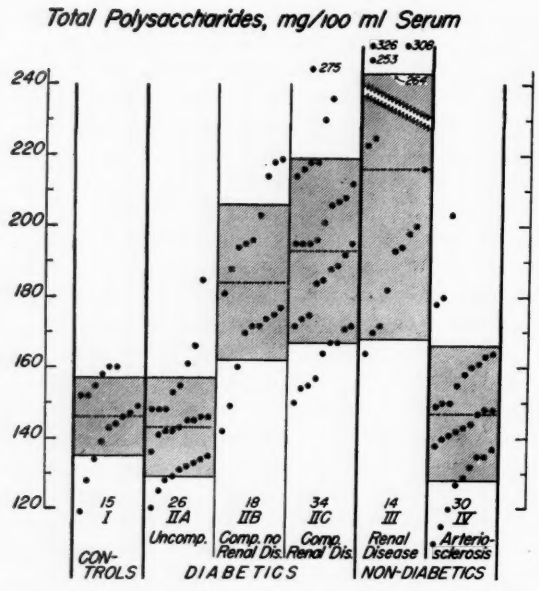

FIG. 1. The total protein-bound serum polysaccharides in the groups of patients studied. The dashed horizontal lines represent the mean in each group. The shaded area encloses the mean±S.D.

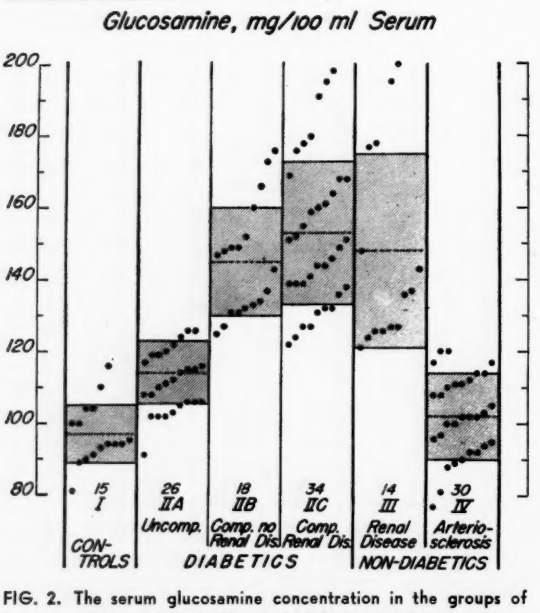

FIG. 2. The serum glucosamine concentration in the groups of patients studied. The dashed horizontal lines represent the mean in each group. The shaded area encloses the mean±S.D.

simply reflects widespread degenerative vascular disease in the diabetic patients selected for study, the elevated serum polysaccharide levels being the result of concomitant tissue injury. The data, however, still permit speculation regarding the possibility of a relationship of increased circulating polysaccharides to the eventual development of deposits of hyaline material in and around certain capillaries in such patients. Certainly they indicate that the serum polysaccharide pattern in diabetic patients with degenerative vascular disease is different from that in nondiabetics with degenerative vascular disease, in whom capillary alterations accepted as characteristic of diabetes occur rarely if at all.

While the number of glomeruli affected and the degree of involvement may vary in cases of diabetic glomerulosclerosis, both kidneys are usually affected equally. McManus has observed that hyaline material is not deposited in ischemic glomeruli.[11] This observation might be explained if circulating polysaccharides were in some way involved in the formation of glomerular hyaline deposits.

Among the autopsy protocols of Montefiore Hospital is that of a diabetic patient who died in 1940 with severe generalized arteriosclerosis. The heart revealed scars of old infarcts, and the left lower extremity had been amputated in 1938 for gangrene. The left kidney was hypertrophied, weighing 400 gm., and revealed widespread severe diabetic glomerulosclerosis and severe afferent arteriolarsclerosis. The right kidney was atrophied, weighing 50 gm., as the result of complete occlusion of the main renal artery by an old calcified arteriosclerotic plug. Not a single glomerulus in many sections which were studied originally and recut subsequently revealed diabetic glomerulosclerosis, and only a very rare afferent arteriole revealed slight hyalinization. This is but one case, to be sure. One possible explanation of the unique anatomic findings is that something did not get into the glomeruli of the uninvolved kidney in sufficient concentration, or over a long enough period of time, to allow the formation of hyaline within them, nor incidentally in their afferent arterioles. While this case also affords a striking demonstration of the close association of diabetic glomerulosclerosis and afferent arteriolarsclerosis, available evidence indicates that factors other than arteriolarsclerosis alone are involved in the production of the glomerular lesion.[9]

The recent report by Sommers, Crozier and Warren,[24] that ultraviolet absorption patterns differing from normal, and varying with the disease, are found in various diseases characterized by hyalinization of glomeruli is of interest in this connection. A specific

pattern was detected in all glomeruli of kidneys with diabetic glomerulosclerosis, independent of the degree and type of involvement. Even histologically normal glomeruli in such kidneys revealed a characteristic ultraviolet absorption which "allowed identification of a kidney from a diabetic patient with greater certainty and ease than by conventional methods." The explanation for this phenomenon tentatively offered by Sommers and his associates is based on considerations of specificity of the state of abnormal protein and protein-carbohydrate complexes involved.

The significance of elevated serum polysaccharides as one factor in influencing the morphologic features of diabetic capillary lesions remains to be determined. While the fact is that their pathogenesis is unknown, our observations support the concept of Warren and LeCompte that a disturbance of polysaccharide metabolism may be a common denominator in the pathology of diabetes.[25]

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DISCUSSION

IRVING GRAEF, M.D., (*New York*): I have had an interest in this particular phase of the pathology of diabetes for many years, and Dr. Berkman has given us an excellent summary of new data supporting the view that Kimmelsteil and Wilson originally offered, namely, that there was a specific change in the glomerular capillaries which was not common to any other disorder, and which they found exclusively in diabetics. As you know, there was great controversy earlier among pathologists as to the specificity of the glomerular changes. The identification of retinopathy with glomerular change and the new chemical data provided by the studies from Montefiore and other laboratories have shown us, I believe, that in what we call diabetes mellitus there is at least a group of patients who may exhibit a spectrum-like series of changes, varying from focal to diffuse, involving specifically the glomerular capillaries, the renal arteries, and the retinal capillaries.

Why some diabetics show retinal changes and no glomerular changes I do not know. It seems to me that

Nature provides questions for us when we separate the findings and look at them objectively. If we are agreed that glomeruli of the type shown today are specific for some diabetics, then it seems that the time has come for a change in our terminology and for recognition of the fact that diabetics with these changes are different from those without them.

The tendency, as you all know, has been to oversimplify our problems in medicine and to link things together when they have a superficial similarity. Everyone with sugar in the urine certainly is not necessarily a diabetic by standards involving an appraisal of their capillaries. However, there is a broader appreciation of the fact that the capillaries provide an area of change which must be assessed from the beginning of the recognition of diabetes.

The term "malignant vascular disease in diabetes" has been used by some. Everyone here, I am sure, has had the experience of encountering, especially in juvenile cases, an accelerated disease process in which the disturbance in carbohydrate metabolism is not the major problem. Indeed—I am sorry to say this—control of diabetes or the carbohydrate disturbance seems to have little to do with the course of this disease, and so it behooves us, on clinical grounds as well as pathologic grounds, to recognize the importance of the widespread capillary changes in some diabetics. Why they develop the disease, the role of the endocrines in these individuals, whether or not there is an inborn trait, hereditary factors—these are questions for our further consideration.

I should like to close by asking Dr. Berkman one question: Have you surveyed the capillaries elsewhere in the body with this method for identification of the carbohydrate-like substance, and if you have, what are the results with respect to focal or diffuse lesions?

ERNST P. BOAS, M.D., (*New York*): I should like to ask Dr. Berkman what, if any, is the relationship between these capillary lesions in the retina and kidney and the lesions of atherosclerosis. In other words, are they commonly associated in the same patient? On a number of occasions Dr. Berkman generalized and spoke of degenerative arterial disease as though he were including both forms of arterial disease, but I am not at all clear as to what, if any, is the relationship between atherosclerosis and these capillary lesions.

LEWIS C. PARK, M.D., (*New York*): I should like to ask Dr. Berkman if he has found these capillary dilatations, or aneurysms in patients receiving large doses of cortisone. Has he made any studies on determination of polysaccharides in these cases?

DR. GRAEF: Dr. Allen, you have studied this lesion in the kidney, especially. Would you like to add your views of it?

ARTHUR C. ALLEN, M.D., (*New York*): I think Dr. Berkman expressed the current situation in most of its ramifications pretty much as we see it, but I am sure that he will not mind my taking issue on some aspects.

It is very important, it has always seemed to me, to decide, particularly in diabetes mellitus, whether or not a given lesion is within stroma between vessels or directly within the vessel wall. That is basic. It is basic, perhaps, in terms of future rationale of therapy; it is certainly basic in terms of explaining the deranged physiology of the syndrome of diabetic glomerulosclerosis.

I felt initially, in 1941, that these were lesions of the capillary wall, and I have since had no reason to change my mind in this respect. The polemic on the intercapillary stroma or mesangium about the mesenchyma has increased lately, but I think the most recent work on the ultrastructure of the glomerulus (that of Dr. B. Vincent Hall of Illinois which was reported at the last meeting of the National Nephrosis Foundation) illustrates convincingly the great likelihood that there is normally no mesangium, thus supporting evidence from serial sections that the lesion is truly a lesion of the capillary wall. Of course, as I say, in a disease that is characterized by diffuse vascular sclerosis, as diabetes mellitus often is, the resolution of this issue becomes of considerable importance.

With regard to the retinal lesions, Dr. Friedenwald was generous enough to let me have one of his preparations. So far as I can judge, these retinal lesions appear to be arteriolar or capillary aneurysms of sclerotic, weakened vessels, unassociated, however, in the retina with the type of hyaline spheres that are found in the glomeruli. The aneurysmal part of the diabetic glomerular lesion appears to me to be a secondary component of the lesion. The aneurysm seems to be formed by a dilated capillary, or a series of capillaries about this hyaline glomerular sphere, visualized as resulting from a stenosis of glomerular capillaries by these spheres. These glomerular aneurysms might possibly be the source of the proteinuria that characterizes the syndrome. As you know, dilatation of a capillary causes it to be excessively permeable to protein. In the case of the diabetic glomerulus there is a special stain, a silver stain, which demonstrates a specific laminated pattern of the lesion of diabetic glomerulosclerosis that is observed in no other lesion of the glomerulus. I have not seen any such comparable preparations of the retinal

lesions. I strongly suggest that the retinal lesion is not equivalent to the lesion of the diabetic glomerulus, but rather that it is equivalent, to the lesion in the afferent renal arterioles, probably containing much lipid, unlike the fully developed lesions of diabetic glomerulosclerosis.

Dr. Boas' question is particularly pertinent because he wants to know whether this is truly a sclerotic process, in the broad sense alluded to by Dr. Bevans. I surely think it is. One of the most intriguing things that I have learned here is the crucially important case which Dr. Berkman described in which there was absence of lesions in one kidney marked with renal arteriosclerosis and their presence in the opposite kidney with less obstruction of the main renal vessels. However, I prefer to believe that altered renal hemodynamics had something to do with the immunity of that kidney, just as it may in a kidney that has a Goldblatt clamp on it. As you know, such a unilaterally clamped kidney is relatively spared parenchyma arteriosclerosis.

In answer to one other question, as I indicated in 1941, I did look for capillary lesions in the gangrenous extremities of patients with diabetes. I found no lesions comparable to those of diabetic glomerulosclerosis.

Finally, it has been asked whether glomerular aneurysms occurred in patients given an excess of cortisone. I have seen identical aneurysms in a patient who required an abundance of cortisone, and, recently, in patients who have been bitten by snakes; similar aneurysms appear to have been produced experimentally.

DR. BERKMAN, (*concluding*): I think my experience has been quite like that of Dr. Allen. All of us have been intrigued with the possibility of finding such lesions elsewhere—Ashton, Friedenwald, and others. I knew of Dr. Allen's studies. We have looked in the brain, and in other tissues. Perhaps it is because we do not know how to look, but so far we have not found lesions analogous to those described, with, of course, the exception of the hyalinization in the islets of the pancreas. There again, the same problem comes up which is implied by Dr. Boas' question: What is the relationship of these lesions to atherosclerosis?

I should have made it very clear that I have never seen a patient with any of these renal capillary lesions in whom there was no evidence of arteriosclerosis and arteriolosclerosis. Capillary lesions did not occur as isolated phenomena. Whether this necessarily implies an identity of etiology or pathogenesis, I do not know.

Dr. Park, I think the experience of Dr. Allen of seeing aneurysms in states other than diabetes is borne out by other observers. I have not personally seen them clinically. I, too, have had made available to me through the courtesy of Dr. Friedenwald some of his preparations of lesions in the kidney and in the retina induced experimentally. I have seen nondiabetic cases of our own treated with cortisone in whom there were lesions in the renal glomeruli which we wondered about—whether they represented the lesions that Arnold Rich has seen in patients and in rabbits treated with cortisone. I am not at all sure they are the same as the Kimmelsteil-Wilson lesions. I think all these lesions do reflect some fundamental injury of the glomerular capillary wall, particularly of the basement membrane. The local deposition of protein probably follows independently of the formation of aneurysms and of local sclerosis of the vessel wall.

I cannot answer the question whether there is a mesangium in the glomerulus of the human kidney. In a current journal there is a paper by a very competent morphologist which states unequivocally that the diabetic lesion is intercapillary. Another paper in the same issue asserts unequivocally that it is not, according to another qualified observer.

There must be some relationship between the renal glomerular lesion and hypertension, as Dr. Allen has pointed out. I suspect that there are hemodynamic factors which are involved in the development and eventual evolution of the glomerular lesion, and yet Dr. Allen well knows that characteristic nodular lesions, about the specificity of which both he and I would agree, occur in diabetic patients who, to the best of our ability to determine, have never had hypertension.

I am not talking about equivocal cases of patients who have scars in their hearts, or other anatomic or clinical evidence suggesting that they have antecedent hypertension. Specific capillary lesions can occur both in the retina and in the glomeruli, in the absence of hypertension.

DR. GRAEF: I should like to return to the question Dr. Boas asked, because I think this is a point of departure in our thinking and bears strongly on the rest of our program. We have heard discussed, and have all seen, changes in the capillaries which have some features that distinguish them from changes in the larger vessels. Changes in the distribution of these lesions have been referred to by Dr. Bevans by a suggestion that there is a kind of segmental distribution with sparing of the cerebral vessels and more involvement of the vessels of the lower parts of the body. I need not remind you of the physiologic considerations.

SUMMARIO IN INTERLINGUA

Le Morphogenia de Lesiones del Vasos Capillar in Diabete

Le morbo degenerative de vasos sanguinee que occurre in patientes con diabete a longe durantia es characterisate per alterationes distinctive in capillares retinal e glomerular. Le lesiones capillar de glomerulosclerosis diabetic e de retinopathia diabetic es ric in hyalines continente hydratos de carbon. Le morphologia de iste lesiones es discutite. Es presentate datos que supporta le conclusion que le concentration de polysaccharidos ligate a proteinas es significativemente elevate in patientes diabetic con morbo degenerative de vasos sanguinee in formas que es clinicamente detegibile. Le possibilitate de un relation inter un disturbate metabolismo polysaccharidic e le evolution de lesiones de vasos capillar in patientes diabetic es discutite in connection con observationes facite in un caso de unilatere glomerulosclerosis diabetic.

Reversal of Protein Catabolism

We have shown that destruction of protein is reversible not only in cases of cholecystectomy and gastrectomy, where a possibly preexisting hypoproteinia may facilitate reversibility, but also in herniotomy and appendectomy. In the herniotomy cases, the patients were normal except for a structural defect, while in the appendectomy cases an acute local inflammation in a hitherto normal person would be expected to worsen the catabolic response. Co Tui, on the basis of work on oral amigen, a product of fairly uniform composition, has postulated a specific range of nitrogen intake for each disease. This postulate would, of course, not be verifiable with native proteins with their heterogeneous composition, but should be verifiable with pure amino acids as used by Rose.

The example of intakes of as high as 20 gm. of nitrogen resulting in precarious positive balances has been cited as supporting the irreversibility thesis. A moment's reflection will show the weakness of this argument. It is conceivable that, in a specific disease, a larger amount of one or more specific amino acids is required than is furnished by the proteins represented in the 20 gm. of nitrogen. In that case, a positive balance would not be possible.

Starr *et al* showed that patients in positive balance during a limited experimental period manifested, on the average, greater efficiency and showed fewer abnormal complexes in the ballistocardiograph, than those who had been in negative balance.

Werner and associates have confirmed Co Tui's findings in cases of gastrectomy and fractures of long bones. While the Werner group is inclined to doubt the presence of an endocrine factor, the work to date on the secretion of corticotropin and cortisone in stress leaves little doubt that these hormones play a significant role.

Support against the irreversibility thesis is forthcoming from two other sources. Engel *et al* have shown in the fasted animal that the protein catabolic response to either adrenal cortical hormone or stress can be abolished by adequate administration of carbohydrates and amino acids. And Madden gave a mixture of amino acids containing radioactive methionine intravenously to experimental animals with the acute injury of a turpentine abscess and found that under these conditions radioactive sulfur in comparable amounts appeared in the tissues both of the experimental animals and controls.

As an editorial in a recent issue of the J.A.M.A. expressed it: "There seems little or no support for the idea that amino acids after injury are useless in protein nutrition and that if given they merely act as a source of energy. . . . Food is an important requirement under most, if not all, conditions and protein seems no exception to this rule."

From "Review: The Fundamentals of Clinical Proteinology" by Co Tui, M.D., in *The Journal of Clinical Nutrition,* March-April, 1953.

Metabolism of the Serum Lipids in Diabetes and in Arteriosclerosis

George V. Mann, M.D., Boston*

As an experimentalist interested in arteriosclerosis, I look upon diabetes mellitus as a natural experiment in atherogenesis. This narrow view may distress clinicians engaged in the management or prevention of diabetes, but they should agree that progress in the prevention of atherosclerosis will benefit diabetic human beings most of all.

In 1947 I began a laboratory study of the effect of experimental diabetes on the development of vascular disease in animals. The premise that the presence of diabetes aggravates the vascular disease is so attractive that even after five years of fruitless work it is sometimes tempting to try again. It was not possible to demonstrate that this was a valid hypothesis. Although certain capillary lesions were demonstrated in diabetic rats, no evidences of major vessel disease were produced in either rats, dogs, or monkeys, whether fed cholesterol or not.[1]

A second hypothesis concerning atherogenesis has been studied and contested for almost half a century and yet has eluded the critical experiment which will properly evaluate its verity. In simple terms this hypothesis states that atherosclerosis, a variant of arteriosclerosis, is a consequence of abnormal lipid metabolism. The immediate problems posed are those of describing the kind and extent of abnormal lipid metabolism necessary for this consequence, a description of the contribution or weight of abnormal lipid metabolism in this effect, and finally a description of the mechanism by which the lipid abnormality develops. There is now a great deal of acceptable information on these points, but for the present I shall consider some evidence that my associates and I have obtained in studies of diabetic human subjects. If from the relation of these observations, any suggestions or implications are made for the management of diabetes, they are fortuitous.

With the cooperation of the Joslin Clinic and others, we have collected an array of measurements of the serum cholesterol and beta-lipoproteins in human diabetic subjects of various clinical descriptions. Much of this descriptive material has been published with Keiding and associates.[2] Such material is, of course, qualified by the validity of the clinical information and the reliability of the laboratory measurements. Most will agree that the Joslin Clinic excels at careful and systematic follow-up of patients, and I have documentation of the laboratory performance with which I am prepared to convince those skeptical of the second assumption.

In the beginning it should be emphasized that there is no distinctive lipid level, or pattern of lipid levels, characteristic of diabetes. Neither the cholesterol nor the lipoprotein levels as measured with the ultracentrifuge—and that method has the greatest resolving power of all those currently available—are unique for diabetes. Any differences that appear are reflected as differences in the statistical summaries of groups of people. This is true even of subjects with severe diabetic acidosis. We cannot diagnose diabetes or its complications solely by serum lipid information.

We are concerned in this discussion with four measured entities: the concentrations of serum total cholesterol and of three bands or classes of beta-lipoproteins which are designated $S_f12\text{-}20$, $S_f21\text{-}35$, and $S_f35\text{-}100$. A summary of these concentrations for randomly selected groups of United States males and females by age is shown in figures 1 and 2.[3] There are three characteristics that should be pointed out. First, it is demonstrated that these concentrations are dependent on age and that the data describe a parabola which shows a maximum in the fifth and sixth decades for males and females, respectively. Second, until about the age sixty, when the curves for the two sexes cross, the females

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A portion of this work was done while the author was an Established Investigator for the American Heart Association.

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tend to have lower levels of each quantity. Finally, we must not neglect the consideration that while we call these subjects "normal" as adjudged by conventional criteria, almost all of them are in fact afflicted with atherosclerosis in variable degree. It is useful, however, to compare with these data the measurements obtained in a population of diabetic patients. This requires the reasonable assumption that the diabetic subjects are drawn from the same population.

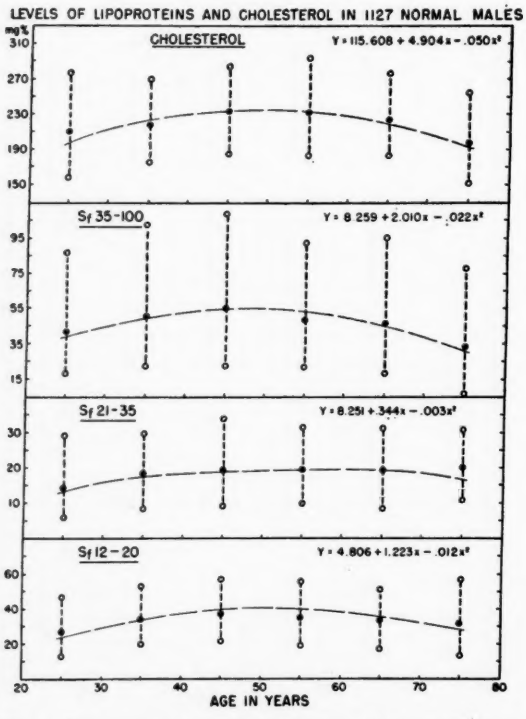

FIG. 1. The means and standard deviations of the distributions shown have been computed after a logarithmic transformation of the observations ($x' = \text{Log } x$). This procedure largely eliminates the skewing of the distributions which would interfere with statistical evaluation. The transformed values obtained have been returned to arithmetic proportions for this graph. The regression equation for each quantity was derived by the method of least squares.

Examination of about 250 diabetic subjects showed similar values. As with the nondiabetics, the mean levels were age-dependent and showed a generally parabolic curve, with the maximum a few years later in females than in males. The same sex difference of level seen in the normal subjects was present. The mean levels in the diabetics were slightly higher than those in the

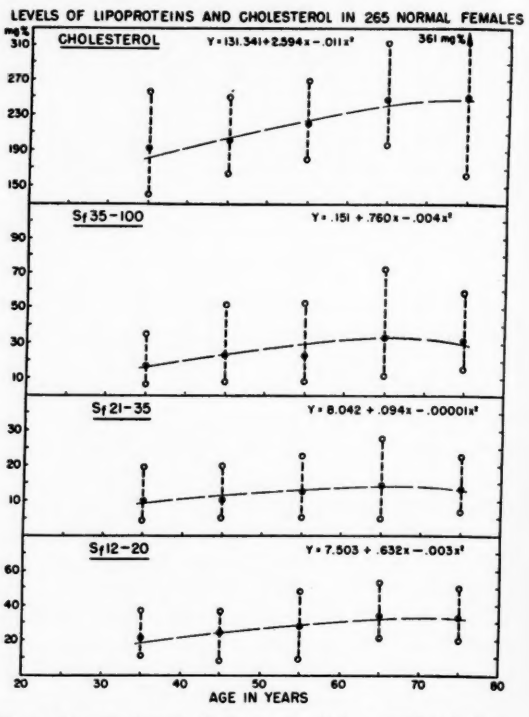

FIG. 2. See the legend for figure 1 which is applicable here.

normals. The variance was large, however, and while we can show significant differences of means if the numbers of measurements are sufficient, we cannot show this for small groups, and we can almost never make reliable implications concerning the status of the diabetes from this information. When one considers that this sample of diabetic subjects included many ages, degrees of severity, and qualities of control, it is clear that interpretation of such pooled data is almost impossible. Still it seems important to identify the reason for such small differences as were demonstrated. The subjects were grouped according to the severity of diabetes, using daily insulin dose as a criterion without evidence of correlation of this attribute with lipid levels. When the subjects were arranged according to the duration of diabetes, only small and apparently trivial correlations were found.

When 144 diabetic subjects who had been completely studied were considered according to adequacy of control, there was a suggestion that good control was characterized by lower serum lipid levels than was poor control (figure 3). The difficulty here is the evaluation of control, for, while we have defined these grades of control according to objective clinical events, the classification still depends in part on subjective judgments of

FIGURE 3

Mean lipoprotein and cholesterol values in 144 diabetic patients related to the degree of control of the disease.*

Degree of Control	No.	S_f 12-20 mg%	S_f 21-35 mg%	S_f 35-100 mg%	Cholesterol mg%
Good	19	42(31)†	21(16)†	24(22)†	242(231)†
Fair	29	42	20	26	223
Poor	96	55	33	45	256

*Previously published in DIABETES *1*:437, Nov.-Dec. 1952.
†One case of familial hypercholesterolemia excluded.

both the patient and the physician. One may be duped by a sophisticated patient who tells his physician what the latter wants to hear. We were left here with one clue. This was the suggestion that poor control of diabetes was associated with higher lipid levels.

A consideration of the relationship of the complications of diabetes to the serum lipids was revealing but difficult to interpret. In figure 4 the data for S_f12-20 lipoproteins and cholesterol indicate that the presence of peripheral vascular calcification had little relation to the serum lipid levels. The presence of retinitis, however, was associated with a pronounced increment of the S_f12-20 class of lipoproteins. Is this a causal relation? The answer is complicated by the influence of diabetic nephropathy on serum lipid levels. Patients with nephropathy have greatly increased levels of all classes of lipids studied. Here again, we are at an impasse, for we cannot determine whether this lipemia is a cause or an effect of the nephropathy.

Our studies turned then to what seemed a more

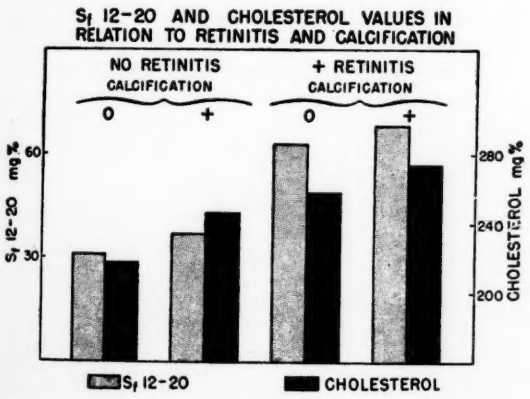

FIG. 4. Comparison of the increase in S_f12-20 class of lipoprotein and cholesterol values in 144 diabetic patients arranged according to presence or absence of retinitis and arterial calcification. Previously published in DIABETES 1:439, Nov.-Dec. 1952.

manageable experimental situation. Having been impressed by the serum data of a boy in diabetic acidosis and exhibiting lipemia retinalis, we began, with Dr. Elizabeth Tuller of the Joslin Clinic,[4] a study of serum lipid patterns in diabetic acidosis and the influence of treatment on these levels. Figure 5 illustrates the remarkable changes observed in the first patient when

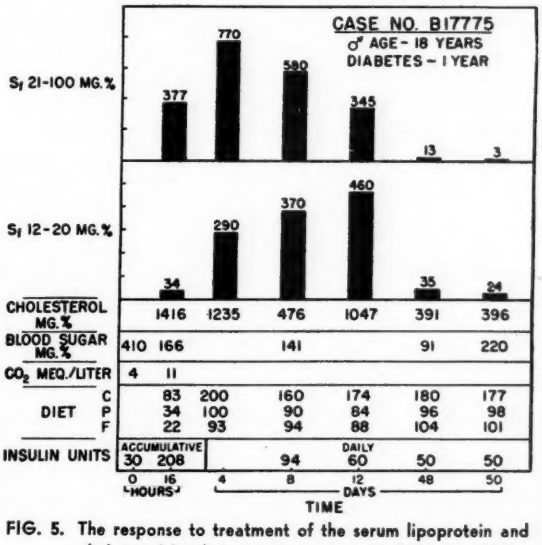

FIG. 5. The response to treatment of the serum lipoprotein and cholesterol levels in a young man with diabetic acidosis. Previously published in DIABETES 3:279, July-Aug. 1954.

treatment was commenced. We then undertook serial studies in patients appearing in the clinic for treatment of diabetic acidosis. We have studied 18 such cases in some detail. Six of these were classified by Joslin's standard, as acidosis ($CO_2 > 9$ mEq./L.) and twelve as diabetic coma ($CO_2 \leq 9$ mEq./L.). We found a relationship between the severity of the acidosis as measured by the plasma carbon dioxide content and the serum lipids, but this was far from linear and suggested the presence of other important factors (figure 6).

In eleven other cases, the response of the serum lipids to conventional treatment of diabetic acidosis was similar in quality to that seen in the first case, although never so dramatic. Visible lipemia was variable in the remaining subjects. There was commonly a gross elevation of the S_f12-100 classes of lipoprotein, and these quantities sometimes showed a paradoxical transitory increase with treatment. We interpret this to represent a release or transfer of low density material in the S_f100 and higher classes, which then traverses the lower S_f classes on its way to cellular utilization. This interpretation implies that diabetic acidosis produces a block of the normal

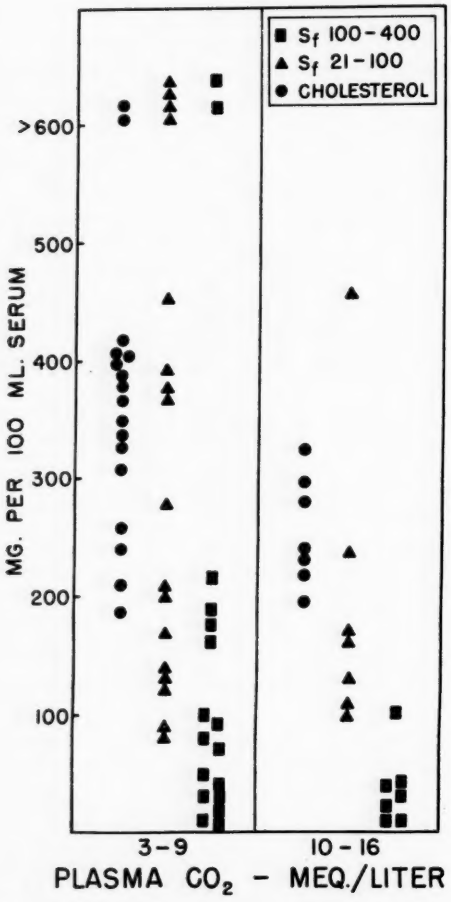

FIG. 6. The relationship of the degree of diabetic acidosis to the level of serum lipids. Previously published in DIABETES 3:281, July-Aug. 1954.

transition of lipid materials from low- to high-density blood complexes. There was also the notable fact that several of these young subjects never attained the low levels of all or some of the lipid quantities which we would expect nondiabetic subjects of their descriptions to show. We could not relate this to persistent lack of control, although we suspected that as a cause. Some of these subjects showed early signs of diabetic complications and, as we have shown, this in itself is associated with abnormal serum levels.

Having satisfied ourselves that these concentration changes were in excess of those attributable to changes of hydration, we are confronted with the need for a plausible explanation. An intriguing possibility is this: Diabetes mellitus is associated with an abnormality of lipid catabolism which is manifested in the extreme during diabetic acidosis. One consequence of this defect is an accumulation of lipids as low-density (high S_f) lipoprotein aggregates in the serum. This accumulation, whether large and of short duration or small and of long duration, contributes to the atherogenetic process in proportion to the product of these dimensions. The cumulative effect of these episodes over a decade results in the vascular disease we commonly see in diabetic subjects. This explanation poses two questions of practical clinical importance:

Are the conventional measurements of carbohydrate metabolism adequate criteria for the clinical management of diabetes?

Is the kind of treatment with diet, insulin, and exercise which is given diabetics to be judged by freedom from coma and gross acidosis or is there some more subtle measurement which should determine the treatment?

Finally, these observations of human diabetes suggest that this disease may be a fruitful place to widen our understanding both of lipid metabolism and atherosclerosis, whether the two are intimately related or not.

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[3] Measurements obtained during the participation of this laboratory in the Cooperative Study of Lipoproteins and Atherosclerosis, sponsored by the National Advisory Heart Council, National Institutes of Health, Bethesda, Maryland.

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DISCUSSION

THOMAS H. MCGAVACK, M.D., (*New York*): In a field of endeavor beset with a bewildering maze of data, from which it has as yet been impossible to synthesize a concerted whole, Dr. Mann should be complimented upon the directness and clarity of his presentation.

A rather long-continued, though perhaps not well sustained, interest in blood lipids began some twenty-two years ago when Dr. Irving Chaikoff helped us study the blood fats of normal, diabetic, and xanthomatous

subjects before and after the use of fatty meals. Several facts stand out in this early work which are of interest in connection with Dr. Mann's presentation.

In the first place, the postabsorptive blood fat partition of normal subjects, including total fatty acids, total lipids, total cholesterol, and cholesterol esters, remained remarkably constant when spot-checked repeatedly over a period of several months. This was in sharp contrast to the blood fat levels of subjects with idiopathic hypercholesterolemic xanthomatosis and not fully controlled diabetes mellitus, which, in the individual patients, varied considerably from time to time, the greatest variation appearing in the fatty acid and phospholipid rather than in the cholesterol content of this serum.

It was further noted that the percentage of total lipids present as cholesterol in a case of xanthomatosis was always lower than normal. Parenthetically, it may be added that this patient died of severe myocardial failure associated with atherosclerotic lesions affecting the coronary arteries; similarly advanced lesions were present in other medium-size and larger arteries.

It was also clear from these studies that recession of the visible xanthomatous lesions could be obtained by low calorie diets, irrespective of the presence or absence of considerable amounts of fat, with a consequent marked reduction in total serum fat but little change in the cholesterol fraction of blood lipids.

Our second concerted study of blood fat was made about ten years ago, when we tried to correlate the level of blood lipids with the status of our patients in diabetic coma. We observed wide hourly fluctuations, similar to those seen in Dr. Mann's case of the boy in diabetic acidosis, who was also suffering from lipemia retinalis; these changes could not be in any satisfactory manner related to the control of the acidotic state.

Dr. Mann's studies have thrown considerable light on these earlier studies in relationship to the pathogenesis of atherosclerosis. Both our xanthomatous patient and the diabetic patients probably had episodes of lipemia associated with flooding of the blood and tissues by large concentrations of S_f100-400 particles. These may subsequently have become incorporated into material of the S_f12-20 class, which under favorable conditions might have been deposited within the blood vessel walls. This, I think, begins to show a dividing line even more clearly between the senile type of arteriosclerosis and the atherosclerosis present in diabetes mellitus.

The third piece of work concerned with blood fat, which I have had the good fortune to follow at close range, is that of Dr. Allen Goldbloom and his associates. That portion of his study concerned with seventy-five patients between eighty and one hundred years of age is of particular interest here. Like Dr. Mann, Dr. Goldbloom observed a decline with age in serum cholesterol and in all S_f lipoprotein fractions from 12 to 100. In addition, Dr. Goldbloom recorded a corresponding decline in total and other lipid fractions as also in the S_f material with densities from 100 to 400. These changes took place despite a rising incidence of thoracic aortic calcification observed roentgenographically and increasing atherosclerotic changes present in gross and microscopic post-mortem examinations. In this group of patients between sixty and eighty years of age, 37 per cent of the men and 54 per cent of the women had calcification of the aorta, as contrasted with 58 and 87 per cent, respectively, for the group between eighty and one hundred years. In other words, patients between eighty and one hundred years old showed a continuous increase in arteriosclerosis, although they had a low atherogenic index and low values for Svedberg flotation units between 0 and 12, and 12 and 400.

Hidden away in Dr. Mann's paper is a further intriguing thought, based on the fact that several of the young subjects on recovery from acidosis and for considerable periods thereafter (up to several months) never attained blood lipid levels commonly expected in the nondiabetic subjects. Lack of control was thought to be the cause. This poor control is common enough, but we have seen good control in the ordinary sense of the word—normoglycemia and aglycosuria—associated with these aberrations in fat metabolism. Moreover, it is common knowledge to find some of our most severe arterial lesions in those subjects whose diabetes has always been mild in terms of carbohydrate tolerance and insulin requirement. Even if we finally recognize the atherosclerosis of diabetes, xanthomatosis, and other diseases such as nephrosis, associated with high serum lipid values as due primarily to the metabolic fault, it should be stressed that we probably cannot place the arteriosclerotic lesions of aging individuals in the same category. Many factors enter into the development of the arteriosclerotic and atherosclerotic process.

In closing, several points concerned with this whole question of the etiology of arteriosclerosis need to be emphasized.

Looking for *the* cause of atherosclerosis will continue to blind the individual investigator, who must of necessity work in a restricted field.

Many technics and many disciplines have been brought to bear upon the subject of the etiology of atherosclerosis during the last half-century. Some examples readily come to mind: (1) the production of atherosclerosis through

(a) feeding experiments, (b) local blood vessel damage, and (c) hormone administration—particularly the catecholamines; (2) studies of blood and tissue lipid by Cohn fractionation, Svedberg flotation, chemical partition, chylomicron counts, venoarterial lipid differences, and so forth; and (3) clinical analyses of data in arteriosclerotic patients and those suffering from metabolic diseases associated with readily appraised alterations in lipid metabolism, such as nephrosis, xanthomatosis, and diabetes mellitus. There has to date been no satisfactorily comprehensive and critical review of the vast store of data obtained by these different disciplines. Moreover, all too infrequently no single series of cases has been subjected to the application of several avenues of approach consecutively or simultaneously. It is a pity that those active in this field cannot so consolidate working teams and resources as to make a simultaneously broad and intensive survey and investigation of a statistically significant group of human subjects.

Finally, what does apparently emerge from the mass of data already collected is the fact that (1) fat metabolism and atherosclerosis are indelibly related; (2) some tissue factor or factors altering the vascular wall is as important in the pathogenesis of atherosclerosis as the alteration in lipid fractions; and, (3)—may I emphasize a point to which Dr. Mann has already alluded—no therapeutic suggestions can be deduced from the work thus far accomplished.

C. F. WILKINSON, M.D., (*New York*): I shall stress a factor or an approach to atherosclerosis and even diabetes that is frequently overlooked; that is, the genetic factor that is involved and the interplay in various inherited characteristics.

Diabetes can be inherited as a recessive or as a dominant trait. As is common with most diseases when inherited in either of two ways, the recessive characteristic occurs early and is usually more severe. Many of us feel that "uncomplicated" atherosclerosis is also an inherited factor that may be also inherited in one or more ways.

Certainly, hypercholesterolemia is an inherited factor, and many other conditions which we associate as aggravating factors of atherosclerosis are also inherited factors.

It is fairly well known that many characteristics associated in the same chromosome may be transmitted very closely together and the closer together they are, the harder it is for them to be disassociated in the crossing-over phenomenon. For this reason it is not uncommon, I feel, for a primary hypercholesterolemia to be transmitted with a gene concerned with hypertension, if you will, or uncomplicated atherosclerosis, or either type of diabetes. We should not necessarily confuse cause and effect with aggravation.

It appears to me that in the field of genetics, we still have a long way to go in separating out the different factors that complicate the primary factor for atherosclerosis. Certainly there is more than one type of diabetes, and we should begin to separate the various genetic types and see how they correlate with one another.

DAVID BARR, M.D., (*New York*): For several years I have been studying lipid relationships in diabetics as measured by the Cohn method of fractionation. These are highly variable and cannot be closely related to the severity of the disease. Certainly we can agree with Dr. Mann that diabetes cannot be diagnosed by any single form of lipid pattern. Some diabetics show a high degree of lipid abnormality early in their illness. For instance, a child of four years, without nephropathy, retinitis, hypertension, or recognizable atherosclerosis, had a highly abnormal lipid pattern. On the other hand, many diabetics who require much insulin and are frequently ketotic, and continuously glycosuric may exhibit relatively normal lipid relationships over long periods. I agree with Dr. Mann that in the presence of nephropathy lipid disturbances are usually marked.

In our studies of nephropathy in diabetes, we have been impressed with its similarity to the nephrotic syndrome. In each there is diminution in albumin and large increase in the beta and alpha globulins. In hypercholesterolemia there is marked diminution in alpha lipoprotein and greatly increased beta lipoprotein.

I was especially interested in Dr. Mann's thesis that ketosis leads to disturbances in fat metabolism. It has been our experience that tendency to ketosis and tendency to diabetic hyperlipemia are quite separable and that in particular cases there may be marked accumulation of neutral fat with slight ketosis, or diabetic coma with very little accumulation of neutral fat.

DR. MANN, (*concluding*): It is very easy to demonstrate in cholesterol-fed rabbits that restriction of the caloric intake, keeping the fat and cholesterol intake constant, is followed by an increase rather than a drop in serum lipid levels, as we expected. This happens regularly. We have no idea what the explanation is.

Both Dr. McGavack and Dr. Wilkinson touched on the interesting proposition that it would be injudicious to consider that atherosclerosis can have a single causation. I agree that there must be multiple causes in atherosclerosis. I suspect that an important place to look for another factor is in the elastic tissue system of the vessels.

We have studied the relationship of calorie intake to cholesterol and serum lipoprotein levels. I should like to emphasize that when we took a group of subjects and lowered their caloric intake so that they lost weight we found a reduction in serum lipids only in those subjects who had initial high levels.

SUMMARIO IN INTERLINGUA

Metabolismo de Lipidos Seral in Diabete e in Arteriosclerosis

Le natura del anormalitate metabolic in diabete mellite esseva examinate relative a su possibile signification in atherogenese. Il esseva establite que il existe nulle anormalitate del configuration in le lipidos seral le qual esserea characteristic de omne patientes de diabete. Le nephropathia terminal in diabete es generalmente associate con grossier elevationes del nivellos seral de cholesterol e lipoproteina, sed iste association non poteva esser identificate como un relation causal. Multe patientes de acidosis diabetic exhibi elevationes del nivello seral de cholesterol e lipoproteina. Iste anormalitate es reducite e a vices eliminate per le correction del acidosis. Acidosis diabetic con lipemia retinal es le manifestation extreme del condition. Es exprimite le notion que diabete es characterisate per arteriosclerosis a causa del effecto cumulative de successive episodios de lipemia que resulta, de lor parte, ab variabile grados de noncontrolo del diabete. Mesurationes del metabolismo de hydratos de carbon es possibilemente inadequate indicatores de iste phenomenos.

Characteristics of Diabetics Awarded the Quarter Century Victory Medal

An outstanding and cheerful feature of these patients is that they are asymptomatic—no complaints. What a contrast to the usual diabetic, even after 10 years of the disease! As a matter of fact, since the inauguration of this series not one patient has died, so that in 1953 the average duration of their diabetes is 30 years. Women predominate, 28 to 18. The average age at onset of diabetes is 14.7 years, the range being 2 to 32 years with only 2 patients 30 years of age or older at onset. Of the women, 20 have married and so far have 19 children, and of the men, 15 have married and have 35 children; one of the men now has six children ranging in age from 5½ to 19 years, the youngest having been born 23 years after the onset of his father's diabetes. Heredity is known to be a positive factor thus far in 25 of 42 cases or 60 per cent. Only 54 children from 35 marriages have been born, or 1.5 children per marriage, thus showing that the opportunity for propagation of diabetes is not very great. This is in striking contrast to a recent survey by Dr. Priscilla White who permits me to state that among a hundred children ranging up to 18 years, of 75 diabetic mothers, she found 6 definite diabetics and 5 others chemically diabetic, in addition to 15 who were on the borderline. Among the fathers the figures are less striking.

Searching for light on treatment, it is evident that these patients, particularly the younger ones, went through a Spartan regimen during the first few years they had the disease. Only gradually, after the early period, were their diets increased in carbohydrates and calories, and even if later they became less rigorous, only temporarily did their diets become liberal by modern standards, despite the use of insulin. The diet at present is not known. The dosage of insulin averaged 47 units for 41 cases, the range being 16 to 100 units with 3 patients taking between 80 and 89 units, and 15 from 30 to 40 units. The number of persons who could acquire the Quarter Century Victory Medal should increase by leaps and bounds, particularly because of our better knowledge of diet and the value of exercise and insulin. It is desirable that the number should increase, because each Medal case is a striking example to other diabetics. Each case creates a needed standard. Doctors universally should have their own Medal Cases for their own encouragement. Changes in criteria for reaching the decision as to whether an individual deserves a medal are desirable. It is pathetic to withhold recognition from a patient in whose artery of the ankle there is only a tiny fleck of calcium, because such lesions are so common at middle life in nondiabetics. Perhaps special rules for awards can be devised for diabetics who acquire the disease at the age of 40 years and above.

Elliott P. Joslin, M.D., in *Postgraduate Medicine*, September 1953.

The Capillary Vascular Lesion in Diabetes Mellitus

Its Clinical Manifestations and Significance

Louis Leiter, M.D., New York*

The clinical syndrome associated with the capillary vascular lesion in diabetes stems from two primary sites: the eyes and the kidneys. In each of these locations the vascular lesion is quite specific for diabetes and the clinical consequences are very serious. There is evidence suggesting a common morphologic and biochemical basis for the microaneurysms in the retina and the hyaline deposits in the glomeruli.[1, 2] There is no explanation for the apparent limitation of this process to these two capillary regions in the diabetic human or animal. Clinically, manifestations of lesions in either the retina or the kidneys—usually simultaneously in the two organs—are found in both young and old diabetics. Although these were originally described in the older age group, and with the implication of milder diabetes as the background, careful study of young diabetics with long survival after the onset of diabetes has emphasized the high incidence of the capillary vascular lesion and its dominant role in the morbidity and mortality of the victims.[3-6]

Nearly twenty years have elapsed since the description by Kimmelsteil and Wilson[7] of a clinical syndrome in diabetics with intercapillary glomerulosclerosis. To this renal vascular lesion has since been added the retinal capillary microaneurysm as the specific morphologic expression of prolonged diabetes, not only in man but presumably also in the experimental diabetic animal.[1, 2] The present discussion is limited to the clinical aspects of the renal lesion.

The clinical statistics of the renal vascular lesion in diabetes are well known. While numerically the clinical syndrome is highest after the fifth decade, this is simply because the diabetic population increases rapidly at this period. Percentage-wise and mortality-wise, the syndrome is most prevalent in the third to fifth decades, comprising the patients with onset of diabetes between the first and third decades.[3] Whether one examines the very large autopsy series reported by Bell[8] or the clinical statistics analyzed by Keiding et al.,[6] the predominance of the renal lesion as the major cause of morbidity and mortality in diabetics under age fifty is overwhelming. In the autopsy series of diabetics with glomerulosclerosis who were under age fifty at death, 46 per cent had the nephrotic syndrome and 63 per cent had uremia, in addition to a high incidence of hypertension and of renal arteriosclerosis. In the subjects with a duration of diabetes of fifteen to twenty years and onset before age forty, 75 per cent of the deaths were from vascular, chiefly renal, disease. It is interesting that the other 25 per cent had only minimal vascular lesions—exactly the same percentage with "minimal complications" was found in Keiding's clinical series among the group with "poor control" of diabetes. The incidence of "nephropathy" in Keiding's series of 451 diabetics with onset of diabetes before age thirty and duration of more than ten to fifteen years was 22 per cent, all occurring in the inadequately controlled group. In spite of the frequency of hypertension in the diabetic with capillary vascular lesions, malignant hypertension was very rare—Bell did not find a single instance among 119 cases of uremia in diabetic glomerulosclerosis.

Among the clinical features of unusual interest is the apparent amelioration of the diabetes as the vascular lesion progresses.[9] Diminution in glycosuria can be at times attributed to diminished glomerular filtration. However, reduction in hyperglycemia and intolerance for previous insulin dosage cannot be explained by renal impairment alone. Malnutrition and reduced caloric intake may play a role. The possibility of a metabolic adjustment must be considered, the origin of which remains mysterious.

In contrast to the easier control of diabetes, the management of edema in glomerulosclerotic patients often presents a uniquely difficult problem. This stems from the fact that several powerful edema-producing influences often coexist—hypoalbuminemia, renal insufficiency of chiefly glomerular origin, and congestive heart failure. In the older subjects, the additional burden of local

Presented at the Symposium on Vascular Disease in Diabetes Mellitus sponsored by the New York Diabetes Association, Oct. 14, 1954.

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peripheral vascular disease, both arterial and venous, complicates the treatment of edema. Mercurial diuretics become less and less effective as renal insufficiency increases.

In the beginning, as with every clinical syndrome, a characteristic combination of symptoms and signs was required to establish the diagnosis. These included evidence of diabetes, massive proteinuria, nephrotic edema, hypertension, and renal impairment. Diabetic retinopathy with capillary aneurysms was added later. Soon, however, it became obvious that the complete clinical syndrome was rather infrequent in comparison with the autopsy findings of the specific renal capillary lesion. In diabetics with glomerulosclerosis who were over age fifty, the incidence of the nephrotic syndrome was only 10 to 15 per cent.[8, 10] Furthermore, the complete syndrome usually meant an advanced stage of the disease. Therefore, attempts at refinement of diagnostic criteria followed; these were reasonably successful in the young diabetics, but hardly so in the older diabetics because of the nature of the signs involved. In older subjects, proteinuria, edema, hypertension, and renal impairment—any or all in varying degrees—could result from hypertensive, arteriosclerotic, or pyelonephritic disease, associated with congestive heart failure or other complications. These important signs of the clinical syndrome, therefore, lost much of their value unless the physician was fortunate enough to obtain accurate information on the exact order of their appearance. Early diagnosis of the Kimmelsteil-Wilson syndrome in the older age groups became largely a diagnosis by exclusion, always an unsatisfactory technic.

It is for this reason that the positive finding of doubly refractile lipoid in epithelial cells and casts of the urinary sediment is so helpful in diagnosis of the specific renal lesion in diabetes.[11] Lipoid cells and casts are not found in hypertensive, arteriosclerotic, or pyelonephritic renal disease and are not associated with the urinary sediment of congestive heart failure. In diabetics over age fifty, the incidence of chronic glomerulonephritis, responsible for doubly refractile lipoid in the urine, becomes relatively insignificant and the possibility of renal amyloid is determined largely by obvious chronic tuberculosis. In short, with rare exceptions, doubly refractile lipoid cells or casts in the urine of a middle-aged or older diabetic, when found by an experienced observer, establish the presence of the specific renal capillary lesion. How early in the syndrome this finding occurs still remains to be determined by frequent serial observations in a large series of patients. A relatively simple diagnostic method seems to have been neglected.

While there are suggestive biochemical alterations in the blood of patients with the diabetic vascular lesion, it is not established that these are specific or early enough changes to be of diagnostic value. The increase in the alpha-2 globulin component of the serum proteins is apparently a reflection of proteinuria and protein regeneration, since it is found in other conditions associated with a nephrotic syndrome.[12] By itself, therefore, it can only be used to confirm the presence of significant proteinuria. Long-term serial studies of the levels of alpha-2 globulin in diabetics without proteinuria remain to be carried out. The fact that protein-bound polysaccharides may be closely related to the alpha-2 globulin fraction heightens the interest in this component as a possible factor in the morphogenesis of the capillary lesion.[13] The evidence, however, is still fragmentary.

Another attempt to distinguish the diabetics with the specific vascular lesions from other diabetics involves the estimation of the large aggregate lipoprotein compounds in the serum. Interesting data have been accumulated, although somewhat short of expectations. It is not surprising to learn that diabetics with hypercholesterolemia have markedly increased concentration of S_f12-20 and higher lipoproteins.[14] Furthermore, in young diabetics without glomerulosclerosis, the changes in serum protein fractions, in the cholesterol content of alpha and beta-lipoproteins, and in the cholesterol/phospholipid ratio were similar to those found in nondiabetic atherosclerotic or nephrotic subjects.[15] This common pattern may be related to atherosclerotic vascular lesions but has little bearing on the specific vascular lesion of the diabetic. However, in the few studies reported so far, it has been possible to distinguish diabetics with renal vascular lesions from those without them on the basis of excessive lipoprotein values, even when corrected for cholesterol levels.[14-16] This has been true for younger diabetics also. In this age group, in the absence of gross vascular disease and with reasonable control of diabetes, essentially normal lipoprotein values have been found even after long duration of diabetes.[17] The clinical and pathologic implications of these findings are intriguing but difficult to evaluate because of a certain nonspecificity of the changes and because the vascular lesion of diabetes is not clearly related to the atherosclerosis with which the lipoprotein abnormalities may be largely associated. On the other hand, the possible therapeutic control of the concentrations of lipoproteins and associated lipids may lessen the havoc caused by the combination of atherosclerosis and the capillary vascular lesions in diabetics. We are still far from an understanding of the factors involved. Here again, long-term studies of a large enough number of patients under appropriate controls

should furnish important clues.

The polysaccharide content of the capillary vascular lesion has led to a systematic study of serum polysaccharides in diabetics with and without vascular disease or the Kimmelsteil-Wilson syndrome.[13] Essentially, the various polysaccharide fractions in the serum, whether bound to protein or not, are increased in diabetics with vascular complications and accentuated in those with renal involvement. However, there is no specificity of the serum polysaccharide increases in relation to the type of vascular or renal complication found in the diabetic patient. The stage of the clinical disease at which these biochemical changes are first manifested is unknown at present. The solution of this problem will require prolonged serial studies beginning with uncomplicated diabetes, preferably in younger individuals. It remains to be determined whether the measurable humoral changes are an effect of a structural tissue damage or, perhaps, a precursor of the lesion. The role of renal insufficiency in producing high serum levels of polysaccharides is a confusing factor that must be controlled by appropriate selection of patients.

The recent production by corticotropin and cortisone of retinal and glomerular vascular lesions in diabetic rabbits and rats, resembling those of human diabetics, has stimulated keen interest in the suggested relationship between normal or excessive adrenocortical activity and the evolution of specific vascular lesions in diabetic subjects.[1, 18] While this hypothesis is provocative, clinical substantiation would be a herculean task if it required body fluid assays for various adrenal steroid hormones in patients followed through the development of the capillary vascular lesion. Corollary studies on the course of younger diabetics subjected to adrenalectomy soon after the first detection of vascular lesions should prove valuable in determining the exact role of adrenocortical activity in the progression of the syndrome. Neither of these two approaches is easy practically nor capable of providing a quick answer to pressing clinical problems. Yet they are necessary types of investigation and deserve full support.

The clinical manifestations of the capillary vascular lesion in diabetes are admittedly an index of a fairly advanced morphologic process. What goes on before this is subclinical and somehow a function of time. At least this seems to be true in the young diabetics, in whom the duration of diabetes can be estimated more accurately. It is during this latent phase that the etiologic biochemical changes must be developing. All our clinical acumen should be directed from every possible angle to patients nearing the end of the latent period.

What is the significance of the specific vascular lesion in diabetes? To clinicians and pathologists the fully developed lesion spells visual and cardiorenal disaster for the patient. Diabetic coma has been displaced by the vascular lesion as the cause of serious morbidity and death in diabetics of all age groups except for the very young, or those with only a few years of diabetes. It is no wonder, then, that every detail in the management of diabetes has been carefully scrutinized for a possible relationship to the vascular syndrome. The battle, both tactical and strategic, still rages over diabetic control: of food power versus insulin power, of strict unbending nutritional morality versus sweet dietary reasonableness. But like the cold war, neither side is really open to persuasion by anything but the very hardest facts, and these are difficult to collect through the curtains of our ignorance. So each side confuses the other by skillful semantic definitions of its own as to what is meant by "good control" and tends to overlook the wide community of agreement. In this situation a neutral physician not specializing in diabetes can wonder if there is really any long-run difference between types of "good control" and if "poor control" is not essentially the same thing under both systems. If it is, then everyone is agreed that diabetes should be controlled within practical limits and that in spite of such control certain metabolic phenomena appear in time, to eventuate in serious vascular lesions. The emphasis of our studies then should be shifted from details of "good control" to more basic biochemical research.

It should be noted that the Kimmelsteil-Wilson syndrome is only one of the Four Horsemen of the Apocalypse of the long-enduring diabetic. Whatever, if any, their relationship may be, there are the three other horsemen—coronary atherosclerosis, peripheral vascular disease, and diabetic neuropathy. Since these are prevalent in both young and old diabetics and, in the former, are definitely a function of time, they are regarded, understandably, by experienced students of diabetes as integral aspects of the metabolic disorder rather than as complications of a degenerative type.[19, 20] This attitude tends to unify the varying concepts of diabetes into the viewpoint that it is basically the same disease in all age groups. Therefore, the significance of the specific diabetic vascular lesion lies, primarily, in its challenge to physicians and allied scientists to track down the metabolic prowler to its cellular or humoral lair and render it powerless to damage the sensitive capillaries of the retina or glomeruli. The prey is well hidden at the moment and elusive, but the hunters have faith in their powers, which include imagination, skill and patience, and the hearten-

ing vision of their ultimate reward—the relief of human suffering and the prolongation of healthy living for the diabetic population.

SUMMARY

The age incidence, clinical manifestations, diagnostic criteria and special biochemical alterations in the blood of patients with diabetic glomerulosclerosis have been reviewed in the light of recent concepts of the pathogenesis of the capillary vascular lesion. The problems of treatment cannot be solved until more knowledge of basic biochemical factors is available. Among these, the role of adrenal cortical hormones deserves intensive study.

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SUMMARIO IN INTERLINGUA

Lesion del Vasos Capillar in Diabete Mellite: Su Manifestationes Clinic e su Signification

Certe aspectos de glomerulosclerosis diabetic es revidite in le lumine de recente conceptos del pathogenese de lesiones del vasos capillar. Illos include le distribution del morbo secundo le etates del patientes, su manifestationes clinic, le criterios diagnostic, e specific alterationes biochimic in le sanguine del patientes. Le problema del tractamento non pote esser resolvite usque le subjacente factores biochimic deveni melio cognoscite. Un de iste factores, le rolo del hormones adrenocortical, es specialmente digne de intense investigationes.

Present-day Concept of Diabetic Retinopathy

Isadore Givner, M.D., New York*

The interpretation of the pathogenesis of diabetic retinopathy has changed so much in the past twenty-five years that it is of interest to consider how and why this evolution has occurred. In part the method of sectioning retinas on the flat and the newer staining and injection procedures have given a better picture of the vascular changes. In addition, ophthalmologists have always tried to determine whether findings in related specialties have an application to their problems, and thus advances made in pathology in general have suggested to thinkers in ophthalmology the possibility of applying such knowledge to their own field. We are indebted for much of our present-day concept of diabetic retinopathy to Friedenwald, Becker, Rich, McManus, Ballantyne, Loewenstein, and Ashton.

In recent years diabetic retinopathy has been on the increase, and if we are to get at the basic cause we must seek the reasons for the vascular involvement that is the basis of its development. The lengthening in life expectancy and the stress of present-day living probably do contribute to the increased incidence of visual loss, but if we are to gain in the prevention of blindness from diabetes we must try to remove or neutralize the fundamental pathology; namely, the involvement of the capillaries and venules which is the beginning of the trouble.

The characteristic vascular lesion of diabetic retinopathy consists of great numbers of minute saccular aneurysms in the retinal capillaries. Often the aneurysms are hyalinized. Two possibilities come to mind in regard to their formation: increased capillary pressure or histochemical changes that allow for the development of these aneurysms. In regard to the former, Friedenwald[1] noted in studying histologic specimens of diabetic retinopathy that localized retinal venous occlusions were associated with abundant newly formed capillary collaterals. Aneurysms were not seen in these newly formed vessels, suggesting that increased capillary pressure is not in itself sufficient to cause the aneurysmal dilations. Some abnormal weakness of the wall appears to be essential. Day[2] in a study of polysaccharides in ocular tissue concluded that in diabetic retinopathy the normal polysaccharide pattern of the capillary bed is disturbed and is unlike that of other diseases of the retinal vessels. McManus[3] suggested that the retinal capillary lesions might be the result of a disturbance in mucoid metabolism. It seems possible that some defect in the basement membrane of the capillary may be the immediate cause of the aneurysm. In studies of capillary fragility Barnes[4] found that in 80 patients with diabetic retinopathy, 85 per cent had abnormal fragility. But 48.5 per cent of diabetics with no retinal pathology showed abnormally weak capillaries, indicating that diabetes in itself is associated with increasing capillary fragility. Rutin reversed fragility in only 25 per cent of the cases even if given for eighteen months and longer, and some patients had vitreous hemorrhages while the capillary fragility was normal and they were taking rutin. We still have been unable to define capillary fragility pathologically.

Today it is finally accepted that the picture of diabetic retinopathy is not dependent on hypertension, arteriosclerosis, or atherosclerosis. In keeping with this concept are the findings in the ocular examinations of 286 juvenile diabetics that I have done at Camp NYDA in a two-year study. In no case was there ophthalmoscopic evidence of retinal blood vessel disease, yet nine patients had hemorrhages or pinpoint aneurysmal dilations —1.5 per cent positive findings in patients having no visual complaints. Incidentally, 0.69 per cent (four patients) gave evidence of cataract formation. The absence of exudates or vessel changes other than those observed in the capillaries emphasizes the latter as the earliest change. Friedenwald[1] finds the intraretinal capillary aneurysms, mostly spherical, to be 20 to 30 microns in diameter and hence just at the limit of ophthalmoscopic visibility. Of course the larger ones of 80 to 100 microns are easily seen.

The retinal lesions of the diabetic are closely related to the renal lesions described by Kimmelsteil and Wilson. The latter are often associated with capillary aneurysms in the kidney glomerulus, and the typical globular hyalin, glomerular nodule of Kimmelsteil and Wilson

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may be in fact a hyalinized saccular capillary aneurysm, showing the retinal and renal lesions to be joint manifestations of the same vascular disease. Ashton and Friedenwald[1] found no distinguishing features in staining and histochemistry between hyaline of the Kimmelsteil-Wilson nodule and the thickened walls of the retinal capillary aneurysm. Both have well developed membranes. No other organs have as yet shown these hyaline nodules other than a rare one that has been seen in the brain.

A case of rubeosa iridis diabeticora, seen through the courtesy of Dr. Henry Marks, that came to complete autopsy is worthy of review in this connection.

R. B., age ten, began to have polyuria and diabetes was then recognized. He was put on insulin but was careless with his diet. Twelve years later he was first noted to have capillary retinal microaneurysms, retinal hemorrhages, and exudate. Pulmonary tuberculosis made its appearance. One year later marked vitreous hemorrhage of the left eye was noted. Rubeosa iridis diabeticora followed soon thereafter, associated with glaucoma in each eye. A filtering operation controlled the tension, but recurrent hemorrhages and retinal detachment followed a retinitis proliferans. At the age of twenty-six with a blood pressure of 195/120 the patient went rapidly downhill and died shortly thereafter.

Postmortem examination revealed pulmonary tuberculosis and diffuse glomerulonephritis, with the cortex reduced in thickness. Histologically Kimmelsteil-Wilson disease was diagnosed by Lisa. The pancreas revealed atrophy of the islands of Langerhans.

Patients seen by Lawrence[5] and others have developed diabetic retinopathy during pregnancy, which cleared following delivery. These observations suggested that the increased corticotropin during pregnancy might play a role in the pathogenesis of diabetic retinopathy. Rabbits given cortisone or compound F alone developed Kimmelsteil-Wilson-like lesions, but no retinal lesions were apparent.

Friedenwald and Becker[6] have found, however, that alloxan diabetes in rabbits predisposes these animals to the capillary lesions elicited by cortisone and corticotropin and have in this way produced an ophthalmoscopic picture resembling early diabetic retinopathy. They have therefore suggested that the retinopathy and nephropathy of the diabetic may be the consequence of an increased secretion of cortisone (or related substances) by the adrenals. Their working hypothesis suggests that both the pancreatic lesions and the action of corticotropin in amounts that are excessive for a diabetic are factors in the development of both the diabetic retinopathy and the Kimmelsteil-Wilson lesions in the kidney.

Hoover, Becker, and Winter found that all the diabetics exhibiting adrenal hypofunction were free of retinopathy, and diabetics with retinopathy exhibited more adrenal activity than did the average diabetic without retinopathy.

Further clinical evidences for excessive adrenocortical function in diabetics with retinopathy is suggested by the worsening of diabetic retinopathy by infection and administration of corticotropin, both of which are associated with increased adrenocortical activity.

Patients with diabetic retinopathy also have increased excretion of oxysteroids, indicative of excessive secretory activity of the zona fasciculata of the adrenal cortex. Improvement of diabetic retinopathy has been reported following decreased adrenocortical function induced by adrenalectomy, pituitary necrosis, and testosterone administration.

Becker[6] reported that at autopsy diabetics with retinopathy and Kimmelsteil-Wilson disease, in contrast to patients with uncomplicated diabetes, had 24 per cent heavier adrenals with excessive lipoid vacuolization of the zona fasciculata and an abnormally high incidence of adrenal cortex adenomas.

Experimentally, when corticotropin or cortisone is administered to alloxan-diabetic rabbits the incidence of renal lesions is increased.

Zubrod[7] and his co-workers noted a marked clinical difference between groups of diabetics with and without Kimmelsteil-Wilson lesions. The Kimmelsteil-Wilson group showed a remarkable absence of acidosis even in the presence of marked hyperglycemia. This Becker explains by a relative excess of certain adrenocortical secretions in the Kimmelsteil-Wilson group. The thesis of Zubrod has been disputed by Wilson, Root, and Marble.[8]

Thorn and his co-workers noted the close interdependence between the function of the adrenal cortex and that of the beta cells of the pancreas in man. They pointed out that primary dysfunction of either of these tissues is often correlated with compensatory functional changes in the other. Thus, they described islet atrophy in Addison's disease and decreased adrenocortical activity in some diabetics.

Becker and Hoover performed adrenocortical function tests in living diabetics. The diabetics with diabetic retinopathy had an adrenal cortex responsive to exogenous corticotropin as measured by eosinophil counts, whereas the adrenal cortex of some diabetics without retinopathy responded less readily or not at all to the corticotropin test. This failure to respond, they believe,

must be related to defective function of the adrenal cortex, since the same patients have a fall in eosinophils following injection of cortisone.

In regard to the possible interrelationship of the glands of internal secretion in the production of diabetic retinopathy, one should note the use of testosterone by Saskin and his co-workers,[9] who found improvement in the fundi of some diabetics to whom they administered it. Even though this improvement has not been substantiated in many cases by others, it is a fact that testosterone has been shown to produce atrophy of the hypophysis and diminished adrenal activity in animals. Occasionally diabetics treated with testosterone have diminished daily insulin requirements as would be expected if they were experiencing diminished adrenal activity.

Dysfunction of both the pancreas and the adrenals has effects on the utilization of several of the B vitamins. Insulin is required for the formation of high-energy phosphate compounds and hence indirectly for the conversion of most of the B vitamins into their phosphorylated functionally active forms.

Becker pointed out the interrelationship of vitamin B_{12}, diabetes, and adrenocortical hormones. Vitamin B_{12} labeled with cobalt 60 was found in relatively high concentrations in the pancreas, kidney, and adrenals of experimental rats. Becker's interest was therefore aroused in the relationship of vitamin B_{12} to diabetic retinopathy and the Kimmelsteil-Wilson lesion.

Experimental chronic alloxan diabetes in rats was noted to induce vitamin B_{12} deficiencies and cause excessive retention of a test dose of the vitamin. Cortisone administration to rats mobilized vitamin B_{12} from all tissues and increased its excretion in the urine. This occurred even in the presence of a marked vitamin B_{12} deficiency, thus aggravating the deficiency state.

Symptoms of vitamin B_{12} deficiency are markedly exacerbated by cortisone, and the turnover of this vitamin is greatly accelerated in adrenal hyperfunction. Chow and Becker state that both cortisone-treated animals and human beings excrete far larger fractions of a test dose of vitamin B_{12} than do normals. Some of the symptoms of cortisone intoxication—for instance, thymus atrophy—are reversed by administration of this vitamin. Chow and Becker have tested the capacity of diabetics with and without retinopathy to retain a test dose of vitamin B_{12}. Diabetics without retinopathy excreted in their urine a smaller fraction of the test dose than did normals. Chow and Becker interpreted this as indicating vitamin B_{12} deficiency.

Diabetics with retinopathy excreted as much as or more of the test dose than did normals. This might indicate that these patients were saturated with vitamin B_{12} or that they were unable to retain the test dose because of adrenal hyperfunction. To test this, these patients were treated with testosterone and retested for vitamin B_{12} excretion. In every case greater retention of the vitamin occurred after testosterone than before it. The increased retention was most marked in those patients who showed increased insulin sensitivity after the testosterone; that is, evidence of diminished adrenal function.

Becker, Winter, and Friedenwald[10] tested the influence of vitamin B_{12} deficiency in rabbits on the renal lesions produced by cortisone. Nondiabetic animals on a vitamin B_{12}-deficient diet which were given 7.5 mg. of cortisone daily for two weeks had a much higher incidence of renal lesions resembling the Kimmelsteil-Wilson nephropathy than did animals on a normal diet containing aureomycin and vitamin B_{12} subjected to the same cortisone treatment. The lesions were in fact more severe and abundant than those produced in alloxan-diabetic animals on a vitamin B_{12} supplement diet given the same cortisone treatment. "It would appear, therefore," says Friedenwald, "that one of the convergent metabolic pathways leading to the production of the vascular lesion may be B_{12} deficiency induced by diabetes and exacerbated by adrenal hyperfunction." Becker concludes that deficiency of vitamin B_{12} does not appear to be the sole defect in the pathogenesis of diabetic retinopathy and Kimmelsteil-Wilson lesions, for four reasons:

(1) Although it prevented cortisone-induced renal lesions in some rabbits it failed to do so in others.

(2) Severe deficiency of vitamin B_{12} in rats did not produce renal lesions resembling those described by Kimmelsteil and Wilson.

(3) Intense vitamin B_{12} therapy failed to alter the clinical course of patients with diabetic retinopathy.

(4) Vitamin B_{12} deficiency in pernicious anemia is not usually associated with Kimmelsteil-Wilson lesions or diabetic retinopathy. "There is ample evidence," says Becker, "that B_{12} deficiency cannot be the sole cause of the retinal and kidney lesions." It seems to him more likely that adrenocortical hormones, diabetes, and vitamin B_{12} deficiency act together in producing the lesion by means of their effect on some other deficiency or metabolic disorder.

The diabetic exhibits an increase in plasma lipids. Lipemia is common in alloxan-diabetic rabbits. Increased blood lipids can also be produced by cortisone, and this effect is found in experimental rabbits. In rats, on the other hand, lipemia is not readily elicited either by alloxan diabetes or by cortisone administration, and the

species does not develop retinal or renal capillary aneurysms under the experimental conditions that produce these lesions in rabbits. Pellerman, working on "complement" in the blood, isolated a new serum protein that he and his co-workers named properdin. The properdin levels given in biologic units of the new protein for each milliliter of blood serum were 25 to 50 in rats, 4 to 8 in human beings, and 4 to 8 in rabbits. Of all the warm-blooded animals tested, the rat had the highest level of properdin, and it is well known that this animal is extremely resistant to infection. It is suggested that properdin plays a part in natural immunity. May we not hope that the future will show other chemical differences that can explain pathologic as well as physiologic difference of man as well as animal and show why human beings develop disease? Some believe that a disturbance of fat metabolism may be related to diabetic retinopathy and nephropathy. Renard and Dhermy[11] emphasize the lipotropic factor of the pancreas as important in the development of diabetic retinopathy.

In conclusion, it is stimulating to be working in an era when diabetic retinopathy has been taken out of the category of irreversible pathologic entities and is being approached as an error in metabolism that may be in our day retarded, stabilized, or even prevented.

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DISCUSSION

HENRY DOLGER, M.D., (*New York*): It has been mentioned several times today that the use of corticotropin and cortisone, experimentally or clinically, might be instrumental in the production of diabetic retinopathy. I cannot recall any diabetic patient who received cortisone or corticotropin in whom diabetic retinopathy subsequently appeared. Similarly, I do not believe that diabetic pregnancy is uniformly associated with retinopathy. It is a fact that there is frequently amelioration of retinopathy during pregnancy.

Dr. Leiter mentioned amelioration of diabetes as the Kimmelsteil-Wilson syndrome progresses. Although such patients have been reported as presenting poor glomerular function so that glycosuria could not be detected, he thought it possibly had to do with deficiency factors. Twenty years ago Keith of the Mayo Clinic, in a report on chronic renal disease, mentioned a patient who died of uremia whose pancreas revealed a total absence of beta cells. There was no record of diabetes in the history. This patient might have had diabetes which had become latent. Recently certain patients who had had diabetes twenty-seven years or more lost all clinical evidence of diabetes in the course of terminal uremia; their glucose tolerance tests were also fairly normal. Thus, one must invoke some other factor. It has been postulated that uremia is associated with the breakdown of ground substance, mucoproteins, and the like, substances which might be the factors in the amelioration of diabetes. In other words, materials released from mucoprotein degradation may be the inhibitors of insulinase which according to Mirsky is destroying insulin activity. With this in mind, two years ago I thought of using glucosamine to inhibit insulinase, but the results of the trial were negative. Diabetic patients were given glucosamine in doses of 50 gm. a day. None of them exhibited any improvement in diabetes.

In conclusion, it is possibly in this particular group that we may find the rationale for a new treatment of diabetes. In other words, the patient with Kimmelsteil-Wilson lesions whose glycosuria and glycemia disappear may be manufacturing the material that makes exogenous insulin unnecessary.

GEORGE WISE, M.D., (*New York*): The first point that I wish to emphasize is the reversibility of diabetic retinopathy, particularly in its early stages. I am sure all ophthalmologists have seen this occur spontaneously. While this enhances our hope for an eventual cure, it also necessitates considerable caution in interpreting any clinical therapeutic result.

Young diabetics with early fundus lesions of pure

diabetic retinopathy should be selected in any clinical research. The fundus picture in these individuals is usually purely diabetic and sufficiently simple for accurate determinations of any change from visit to visit. If older patients with more extensive retinopathy complicated by aging vessels, sclerosis, hypertensive changes, and venous thrombosis are used, the picture becomes much too complicated to judge accurately small changes from visit to visit, and thus the data are less reliable.

The second point I wish to emphasize is the importance of the venous changes in diabetic retinopathy as compared with the capillary aneurysm. The latter is the more dramatic recent discovery and has occupied much of our discussion today, but venous changes are far more important from the standpoint of visual prognosis. Most loss of vision in diabetics is due to the venous changes and their sequellae.

Clinically, diabetic venous changes due to endothelial thickening first appear as narrowing or enlargement of the venous blood column. Unless carefully looked for they can be easily missed. Any fundus vein or its branch may be involved, and the phenomenon is often scattered. As the venous lumen narrows and the wall thickens, thin white sheathing may be seen. This can become very marked. Eventually the lumen is occluded and the typical fundus picture of venous obstruction distal to the point of involvement occurs. Retinitis proliferans and vitreous hemorrhage, the causes of the loss of vision in most diabetics, are intimately associated with and secondary to such venous obstruction. Neovascularization or retinitis proliferans occurs in diabetes, nondiabetic venous destruction, Eales' disease, migratory retinal venous thrombosis, and some traumatic cases. The common denominator of all of these conditions is venous obstruction. Thus, the underlying cause of the visual loss in the diabetic does not seem to be quite so much the diabetes in itself as the blockage of the vein. It is of interest to realize how long we went without recognizing the importance of these venous changes. Only very recently has attention been called to them.

The third and last point is in the realm of biochemistry. Two of the common findings in disseminated lupus erythematosus are the "wire loops" of the kidney and the so-called fibrinoid around the smaller arteries. Fibrinoid apparently got its name because, although known not to be fibrin, it was morphologically like fibrin. It was thought originally to be due to a breakdown of the collagen fibers of the vessel wall.

Klemperer and Baer have presented evidence that both fibrinoid and the thickened arterial basement membrane of the kidney glomerulus, the "wire loop," are depositions of protein residue due to the depolymerization of desoxyribonucleic acid protein. The latter is a very important constituent of the nuclear protein and chromatin material of cell nuclei.

I was particularly interested in hearing Dr. Berkman's discussion, because I think that a good deal of very important information is going to come from further work on the ground substance and the derangements in these protein-bound complex mucopolysaccharides.

LEOPOLD G. KOSS, M.D., (*New York*): In advanced diabetic nephropathy the glomerulus occasionally displays not one lesion but two different lesions. One lesion is the conventional Kimmelsteil-Wilson lesion, which is round and takes silver stain very well. The other one stains red in trichrome, is of crescentic form, and frequently surrounds the round lesions of Kimmelsteil-Wilson. This red-stained lesion is in all respects comparable to hyaline arteriolarsclerosis, and the deposits of this material arranged in this fashion are found only in diabetic kidneys. I have named this renal lesion the "hyaline-fibrinoid" material, because it does take all the stains of fibrinoid, yet it displays, in hematoxylin and eosin, the appearance of homogeneous hyaline. It is possible that this material plays a significant role in the rapid downhill course of diabetics with advanced nephropathy. (Arch. Path. *54*:528-47, 1953)

I have been interested in the discussion pertaining to protein polysaccharide complex on one hand and the permeability of the basement membranes in diabetes in general. I have examined about 180 autopsies on diabetics and have found the hyaline-fibrinoid material in a fairly large number of cases. My findings are that this material is found not only in the glomerular location and not only in the markedly altered arterioles, but also—it is not shown in the picture—in the Bowman's capsule and in the basement membrane of the tubules of the kidney, and that it is undoubtedly a polysaccharide protein complex.

In addition, this material is in all respects similar to inspissated tubular casts which may be found in distal renal tubules. Therefore, on morphologic grounds, it is fair to assume that this is the same material. How did it get into the wall of the glomerular loops? Possibly, the permeability of the capillary loop in the kidney is so altered that the protein which comes from the circulating blood has some way of penetrating through the internal limiting membrane and forms this sort of deposit. This, incidentally, is very closely related to some of the findings found in the eyes of diabetics.

A word about lipids in the kidney of diabetics. In diabetic kidneys, the deposits of fat and lipids, as I

have found, are actually a late phenomenon and not an early one. Therefore, the deeply altered kidneys do contain lipids, and thus the diagnosis can be made on examination of urine. In early diabetic lesions of people who died of intercurrent diseases or accidents, and so forth, there is no evidence of lipid in the glomerulus.

SUMMARIO IN INTERLINGUA

Le Concepto Hodierne de Retinopathia Diabetic

Le autor revide observationes clinic e experimental in relation al cambiamentos ocular associate con diabete, le quales currentemente recipe multe attention.

Le lesion vascular que es characteristic de retinopathia diabetic consiste in grande numeros de minute aneurysmas saccular in le capillares retinal. Il es generalmente acceptate que retinopathia diabetic non depende de hypertension, arteriosclerosis, o atherosclerosis. Le lesiones retinal es multo affin al lesiones renal describite per Kimmelsteil e Wilson. Datos es presentate que suggere que le cambiamentos e retinal e renal pote resultar de un augmentate production de hormones adrenocortical. Un interrelation de vitamina B_{12} e le hormones adrenocortical in diabete ha etiam essite postulate, sed il es clar que un deficientia de vitamina B_{12} non pote esser le sol causa de retinopathia diabetic.

Le autor sublinea le potential reversibilitate de retinopathia diabetic, le qual es nunc studiate como un falta metabolic que probabilemente un die on va succeder a retardar, stabilisar, o mesmo prevenir.

Coronary Artery Disease in the Diabetic

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INCIDENCE

More than half of the deaths in the United States today are due to cardiovascular renal diseases, and chief among these is coronary heart disease. Among diabetics this complication is particularly common. Of 3,499 deaths among patients of the Joslin Clinic between Jan. 1, 1944, and Apr. 27, 1951, 2,456, or 70.2 per cent, were considered by the attending physician to be due to arteriosclerotic cardiovascular-renal disease. Of the total deaths 1,627, or 46.5 per cent, were ascribed to arteriosclerotic heart disease. Of 656 deaths during the period 1950 to 1952, 496, or 75.6 per cent, were due to arteriosclerotic cardiovascular-renal disease; 312 or 47.6 per cent, were of cardiac origin.[1]

TABLE 1

Arteriosclerotic heart disease as a cause of death (experience of the Joslin Clinic)*

Period	Total deaths	Deaths due to arteriosclerotic heart disease	
		No.	Per cent
1898-1914	326	20	6.1
1914-1922	836	83	9.9
1922-1936	4,138	1,234	29.8
1937-1943	3,482	1,438	41.3
1944-1951	3,499	1,627	46.5
1950-1952	656	312	47.6

*Compiled by Statistical Bureau, Metropolitan Life Insurance Company.

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In 761 autopsies on diabetic patients at the New England Deaconess Hospital up to 1952, Warren and LeCompte[2] found evidence of myocardial infarction (both fresh and healed) in 178 cases and coronary thrombosis without infarction in 15 additional cases. Thus, infarction occurred in 23.4 per cent and thrombosis without infarction in an additional 2 per cent or 25.4 per cent in all. These figures cannot, of course, be taken to represent the true incidence of fatal coronary heart disease among diabetics in general, but simply the frequency of this condition in a group of diabetic patients hospitalized for various reasons.

In 1939 Root and his colleagues,[3] using material at the New England Deaconess and Massachusetts General Hospitals, compared the incidence of coronary occlusion in 3,400 autopsies on nondiabetics and 349 autopsies on diabetics. In all decades of life concerned, regardless of sex, coronary occlusion was much more frequent in the diabetics. In fact, in the series as a whole, anatomic coronary occlusion occurred five times as frequently in the diabetic as in the nondiabetic group.

Although these studies indicate an extremely high incidence of fatal coronary heart disease in diabetics, they do not give an adequate idea of the extent of involvement of the coronary arteries in diabetic persons in general. A better impression of this is to be found in the careful routine examination of the heart in diabetics regardless of the chief cause of death. Thus, in 110 autopsies of diabetic patients at the Deaconess Hospital between 1940 and 1946, Millard and Root[4] found coronary arteriosclerosis in 108, or over 98 per cent. Similarly, Stearns, Schlesinger, and Rudy,[5] using an injection technic, noted significant coronary disease in about three-fourths of fifty diabetic persons.

TABLE 2

Myocardial infarction and coronary thrombosis in 761 diabetic patients at autopsy (after Warren and LeCompte[2])

		Myocardial infarction				Coronary thrombosis without infarction	Infarcts plus thrombosis	
	No.	Fresh	Healed	Fresh and Healed	Total		No.	Per cent
Males	325	27	35	21	83	5	88	27.1
Females	436	45	24	26	95	10	105	24.1
Total	761	72	59	47	178	15	193	25.4

In recent years attention has been called to the incidence of coronary sclerosis and occlusion in persons under the age of forty years. Although the total mortality due to coronary disease in this age group is not great, it is significant and high enough to be disquieting. There is some evidence that the incidence may be increasing. Enos, Holmes, and Beyer[6] analyzed the findings in 300 autopsies on United States soldiers who had been killed in action or had suffered accidental death in front line areas in Korea. The ages ranged from eighteen to forty-eight years, and in 200 cases in which such data were recorded the average age was 22.1 years. In 77.3 per cent of the hearts there was evidence of coronary arteriosclerosis varying from fibrous thickening to large atheromatous plaques causing complete occlusion of one or more of the major vessels. Observations on patients with long-term diabetes dying at the New England Deaconess Hospital under the age of forty in recent years have revealed a similarly high or even higher incidence of coronary sclerosis, which has been in keeping with arteriosclerosis affecting the rest of the body. Most of these patients however, have died, not of coronary heart disease but primarily of nephropathy of mixed type, which progresses more rapidly. In fact, among 119 patients with onset of diabetes under the age of fifteen dying between 1950 and 1953 (not necessarily at the New England Deaconess Hospital), 63 per cent of deaths were due to renal disease.[7] As a rule, in these patients, diabetic nephropathy was accompanied not only by generalized arteriosclerosis and coronary sclerosis but also by retinopathy, often of advanced degree.

CLINICAL FEATURES

In general, coronary artery disease among diabetics resembles that in the general population. There are certain features, however, which distinguish this complication in diabetes. Certain of these will be discussed briefly.

Age and Sex. The experience of all observers points to the fact that arteriosclerosis, atherosclerosis, and coronary artery disease occur at an appreciably earlier age in diabetics than in nondiabetics. Whether this is due to a greater tendency in the diabetic toward a generally higher level of cholesterol and/or lipoproteins in the circulating blood or to other metabolic insults occasioned by diabetes, or to both of these and other influences, is difficult to say. As for sex, diabetes tends to equalize the discrepancy in incidence which exists between men and women in the general population. To illustrate the sex difference in nondiabetics one may cite the results of a study made some years ago at Mt. Sinai Hospital by Master, Dack, and Jaffe.[8] Among 500 cases of coronary occlusion the ratio of men to women was 3.4 to 1. The average ratio in 2,803 cases diagnosed clinically and reported in fourteen series in the literature was 4.6 to 1. Among 1,241 collected cases diagnosed at autopsy the ratio was 3 to 1. In the series of 500 cases of Master and his co-workers, 30.5 per cent of the cases of coronary occlusion in men occurred under the age of fifty whereas only 23.2 per cent of cases in women took place in this age group.

On the other hand, in the 761 autopsies on diabetics reported by Warren and LeCompte[2] and referred to earlier, 105, or 54.4 per cent, of the 193 patients with fatal coronary heart disease, were women. Since of the 761 patients 436, or 57.2 per cent, were females, myocardial infarction and coronary occlusion were almost as common among females as males. Incidentally, the average age at death of the females was 63.1 years and of the males 61.5 years. The average duration of diabetes among the females was 11.5 years and among the males 12.5 years.

Stearns, Schlesinger, and Rudy[5] report among diabetics over forty years of age coronary artery disease was as common in women as in men. In the patients reported by Root and others[9] the incidence of coronary occlusion was almost as great among the diabetic women as among the diabetic men. Their study indicated that coronary occlusion was twice as common in diabetic men as in nondiabetic men, and eight times as common in diabetic women as in nondiabetic women. This agrees with the findings of others including Clawson and Bell.[9] From an extensive study which included 50,000 post-mortem examinations, these workers concluded that fatal coronary heart disease occurred about twice as frequently among diabetic as among nondiabetic males and about three times as frequently among diabetic as among nondiabetic females.

Silent Myocardial Infarction. Frequently discussed is the question whether myocardial infarcts occur with relatively fewer symptoms in diabetic patients than in nondiabetics. The matter has arisen because from time to time patients have appeared in whom the diagnosis of myocardial infarction was evident either by electrocardiogram or at post-mortem examination without any history of significant pain or other common symptoms. Furthermore, at the post-mortem examination of diabetic patients dying of other causes, it is not uncommon to find scars of old infarcts without a history suggesting them, either in the recent or remote past. Whether this type of situation arises any more commonly in diabetics than in nondiabetics is a question. One must always consider the reliability of the history obtained, and it is our

belief that truly asymptomatic myocardial infarction does not often occur even in diabetics.

Effect of Myocardial Infarction on the Blood Sugar. Certain clinicians believe that myocardial infarction in the supposed nondiabetic person often brings about a rise in the blood sugar with or without glycosuria. Spühler[10] studied the carbohydrate metabolism in thirty-eight patients, aged thirty to eighty-nine years, who had suffered a myocardial infarct. In older patients marked hyperglycemia and glycosuria were observed and glucose tolerance tests indicated diabetes. Those under fifty years of age, however, showed only slight hyperglycemia and glycosuria, and in none of these did the diagnosis of diabetes come into question. Boulin, Uhry, and Kaufmann[11] determined the blood sugar in five patients with myocardial infarcts and observed a transitory elevation which in some instances reached 250 mg. per 100 cc.

Our own experience in this regard is limited, but these suggestions appear sound: (1) In any supposed nondiabetic with myocardial infarction, if significant hyperglycemia and glycosuria persist for more than a very few days, the possibility must be considered that unrecognized diabetes existed prior to the heart attack or that the stress of the infarction has brought latent diabetes to the surface. (2) Sustained hyperglycemia and glycosuria should be regarded and treated as diabetes until proved to the contrary. (3) If recovery from the myocardial infarction occurs, careful follow-up as regards diabetes should be carried out.

TREATMENT

The management of coronary artery disease in the diabetic differs very little from that in the nondiabetic. The same principles of treatment apply to both groups of patients and medication ordinarily used for treatment in the nondiabetic may be used in the diabetic provided due caution is taken as to dosage. Consequently, in the following discussion comment will be reserved for those matters about which there is special interest or disagreement.

Heparin in Angina Pectoris. Some have reported that in those persons, not necessarily diabetic, in whom coronary artery disease is accompanied by an increase in the serum lipoproteins, the use of heparin parenterally will not only bring about a decrease in these blood constituents but will also lessen the tendency to angina and lower the incidence of coronary occlusion. We have had no experience with such therapy in our own diabetic patients and note considerable disagreement in the literature.

Diet. Particularly if the cholesterol and/or lipoprotein content of the blood serum is abnormally elevated, the amount of fat, especially animal fat, and cholesterol in the diet should be restricted. In our own handling of diabetic patients with coronary artery disease, we have limited fat and total calories in order to bring about loss of weight if the individual is obese, as is so often the case. We have not insisted on an extremely low cholesterol diet because of the evidence that this substance can be synthesized readily within the body. In patients on a well balanced diet, it has seemed illogical to prescribe supplements of choline, methionine, and inositol since these substances are so widely distributed in food.

Anticoagulants. The disagreement which exists today among members of the profession regarding the use of dicumarol and other anticoagulants in frank myocardial infarction holds for diabetic as well as nondiabetic patients. In our practice we have used anticoagulants for those patients who when first seen have been most acutely ill, perhaps in shock, those who seem to have suffered the most severe degree of infarction, and those who are much overweight or have a past history of thromboembolic episodes. We have not used anticoagulants in the treatment of most other patients with infarction.

Insulin in Coronary Heart Disease. There has been in the past, and in some quarters still is, an unwarranted fear of the use of insulin in patients with coronary artery disease. Some writers have gone so far as to state that insulin should not be used, and advocates of this policy have maintained not only that hypoglycemia is harmful but also that hyperglycemia might actually be of benefit. Experience has shown that this is an illogical and short-sighted form of management. Naturally, no one would argue that hypoglycemia should be induced in diabetic patients with coronary artery disease. It should be avoided in all patients, particularly in those with angina or coronary sclerosis. Nevertheless, it is entirely possible to treat diabetes adequately and carefully with a restricted diet and insulin without precipitating episodes of hypoglycemia. To the clinical impression that this type of management is beneficial may now be added the results of Goodale, Olson, and Hackel,[12] who studied by coronary venous catheterization the utilization by the myocardium of glucose, pyruvate, and lactate in patients with mild diabetes. The use of these metabolites by heart muscle was significantly reduced when only moderate hyperglycemia was present. When the blood sugar was brought to normal with small doses of insulin, utilization of glucose, pyruvate, and lactate was restored to normal. In experimental coronary occlusion, Himwich, Goldfarb, and Nahum[13] noted a loss of glycogen from infarcted areas and an

outpouring of lactic acid into the blood stream. Their data indicated that in diabetic patients with coronary occlusion insulin and glucose may be of great value.

PROGNOSIS

The diabetic patient with coronary heart disease has in general a poorer prognosis than the nondiabetic individual. The average duration of life from the first attack of angina to death was only two years in 136 fatal cases recorded by Root and Graybiel.[14] Death occurred in 52.5 per cent of these cases during the first year after onset of angina. In fifty other cases studied just prior to 1952 the average length of life after the onset of angina was 1.6 years.

Among the 507 cases of myocardial infarction reported by Katz, Mills, and Cisneros[15] there were sixty-three diabetics. The mortality in the first two months among the diabetics was 50.8 per cent, compared with 26.6 per cent in the nondiabetics.

During the past year Bradley and Bryfogle of our group have studied the prognosis in 102 diabetic patients who during the years 1943 to 1948 were admitted to the New England Deaconess Hospital with acute myocardial infarction. The dates mentioned were chosen in order to allow at least a five-year follow-up in all cases. Mortality figures were divided so as to indicate those deaths which occurred in less than sixty days after the onset of symptoms of myocardial infarction in contrast to those taking place after this period. I am indebted to Drs. Bradley and Bryfogle[15a] for permission to present certain of their as yet unpublished data.

This series of patients included forty-four males and fifty-eight females. There were only three patients with infarction under the age of forty, two males and one female. Only six males and two females suffered their acute heart attack between forty and forty-nine years of age.

The acute mortality, that is, the mortality within sixty days, was 60.8 per cent for the entire group—54.5 per cent for males and 65.5 per cent for females. This strikingly high death rate is more than twice as great as that encountered among nondiabetics and even greater than that reported by others for diabetics.[15, 16] However, in evaluating the Deaconess Hospital experience the following points must be kept in mind: (1) Of the 102 patients, nineteen were known to have had a previous infarction; fourteen of these were included in the acute mortality group. (2) The average age at the time of the coronary occlusion was greater than that in certain other series reported in the literature, being 63.0 years for the entire group, 62.1 years for the males, and 63.4 years for the females. (3) Of the sixty-two patients in the acute mortality group, fifteen died in less than twenty-four hours after admission and an additional seven died in less than forty-eight hours.

In the series of Bradley and Bryfogle, forty of the 102 patients survived the first sixty days. Of the survivors, thirty-one lived one year, twenty-seven two years, and sixteen five years or more.

In analyzing responsible factors, it was found that the prognosis was poorer in the older age groups and in females. The poorer outlook in females may have been related to the fact that hypertension was about twice as common in them as in the males and to the fact that obesity was more common. About half of the females were grossly overweight, whereas 30 per cent of the males were overweight. Pre-existing angina pectoris, known previous myocardial infarction, previous congestive heart failure, and accompanying azotemia were all associated with a poorer prognosis. Of twenty-two patients in whom a previous history of angina, heart failure, or infarction could not be obtained and in whom there was neither hypertension nor obesity, fifteen survived the first sixty days, reducing the acute mortality to about half that of the group as a whole.

There were eleven patients in whom diabetic ketosis and myocardial infarction existed concurrently. All died, five within twenty-four hours after admission. The average age was 67.4 years. Analysis of the history of these patients suggests that diabetic ketosis with its associated profound metabolic disturbances and resulting circulatory changes may initiate an acute myocardial infarction in individuals who are already predisposed because of well advanced coronary artery disease.

CAUSE AND PREVENTION

All observers agree that among persons in the general population coronary artery disease is three or four times as common in men as in women. Furthermore, the difference in incidence is most marked at ages below that of the menopause in women. Myocardial infarction is uncommon in women under the age of forty. This experience has naturally led to the thought that in some way or other estrogens protect against coronary sclerosis. There is some experimental work to support this idea. Pick and her co-workers[17] found that the administration of estrogen to cockerels inhibited coronary atherogenesis even though the chicks were fed a diet containing cholesterol. Studies of blood serum showed that the protection of the coronary vessels was associated with low total cholesterol-lipid phosphorus ratios. Unexplained was the fact that estrogens exerted no prophylactic ef-

fect against arteriosclerosis of the aorta. In later studies Pick and co-workers[18] found that the administration of estrogen caused a reversal of coronary atherosclerosis in cockerels in which it had been induced by cholesterol feeding. The reversal took place despite continued feeding of the cholesterol diet. The authors discuss possible ways in which estrogen may exert its protective effect. Does it induce lipophage activity which effects movement of lipids toward the adventitia and the perivascular tissue? Does it decrease permeability of the endothelium for lipids? Does it exert an effect on plasma lipid-lipoprotein complexes?

Results obtained in chicks cannot be applied directly to man, so that the experience of Rivin and Dimitroff[19] is of interest. These workers compared the incidence and severity of coronary atherosclerosis in men with cancer of the prostate who were given large doses of stilbestrol, women who had undergone castration, and women with cancer of the breast who were assumed to have hyperestrogenism. There was an apparent decrease of coronary sclerosis in the estrogen-treated males and a significant increase in the castrated women. The incidence of coronary disease in the women with cancer of the breast was less than that in normal females.

The above data are cited in some detail because they form the basis for profitable speculation regarding the situation in diabetic persons. Do women with diabetes show a higher incidence of serious coronary artery disease than nondiabetic women because of deficient ovarian secretion? If so, how is this effect of estrogen lack related to other possible causes of premature arteriosclerosis, including the metabolic insult of the diabetes, disturbance of cholesterol and lipid metabolism, hereditary influences, body build and type, physical and emotional stress, and other factors?[20]

Since coronary artery disease is significantly more frequent among diabetics than among nondiabetics, it follows logically that the disordered metabolism of diabetes is in some way responsible. Following this thought a step further, it is our clinical impression, supported by published results of careful and unbiased studies, that vascular complications are significantly more common and extensive in patients whose diabetes has been poorly controlled.[21] In fact, the presence and extent of degenerative changes has appeared to be directly related to the degree of control maintained over the years. Duration of diabetes is important only in allowing a longer period for deleterious influences to exert their effect.

This opinion that careful and continuous control of diabetes is helpful in reducing the incidence and severity of vascular complications has received increasing support in recent years. Added to the experience, published and unpublished, of many clinicians in the United States, there are recent reports of those in other countries who are abandoning former programs of free diets and disregard of hyperglycemia and glycosuria.[22] Thus, on the basis of studies carried out in Sweden at the Växjö Hospital and the University Hospital at Lund, Engleson[23] recommends that dietary restrictions be observed in the management of diabetes, especially as a prophylactic measure against long-term complications. Dunlop[24] of the University of Edinburgh is even more definite:

"As the result of this and my experience of 'free diets' I have returned to my simple diabetic faith. I believe that whatever specific aetiological factors may be causing diabetic degenerative lesions—endocrine, infective, or metabolic—the careful control and aggressive treatment of the disorder over the years is a most important factor in their prevention or postponement. I believe that to obtain good control diabetic diets should not usually contain more than 200 gm. of carbohydrate; that patients should be initially trained in the hard school of food-weighing, for it is only in that way that they learn to appreciate quantities; and that they should report regularly to a diabetic clinic to be assessed as regards symptoms, weight, glycosuria, and occasionally blood sugar concentration, and, depending on the findings, to have their insulin dosage and diet suitably altered."

It would be too much to expect that by adherence to such a program the incidence and severity of coronary artery disease would be precipitously lowered. However, by such management, by the avoidance of obesity, and by attempts at control of other factors known to favor coronary artery disease one may justifiably hope that the mortality from this complication may at least be reduced. Furthermore, there is good reason to believe that lessons learned in the study and treatment of arteriosclerosis and coronary artery disease in the diabetic may point the way toward a better understanding of the problem among persons in the general population.

SUMMARY

1. Coronary artery disease is even more common in diabetic than in nondiabetic individuals, causing almost half of all deaths.

2. Its incidence and severity are greater in younger age groups in diabetics compared to nondiabetics.

3. It occurs about as commonly in women as in men, in sharp contrast to the situation in nondiabetics, in whom the incidence in males is three to four times that in females.

4. Although hypoglycemia should be avoided in any

patient with coronary artery disease, insulin should not be withheld in the treatment of the diabetic condition. Instead, careful treatment with diet and insulin should be carried out as in any diabetic patient. Ketosis may initiate myocardial infarction in an individual predisposed because of well advanced coronary artery disease.

5. The prognosis of the diabetic with coronary artery disease is much poorer than that of the nondiabetic. Of 102 patients admitted to the New England Deaconess Hospital in 1943 to 1948 with acute myocardial infarction, 60.8 per cent died within the first sixty days. The prognosis was poorer in older patients, in females, in patients with hypertension and obesity, and in those with a previous history of angina pectoris, myocardial infarction, or congestive heart failure.

6. Prevention or delay in development of coronary artery disease depends on restriction of fat and calories in the diet so as to avoid overweight, and upon careful, continuous control of the diabetic condition.

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DISCUSSION

GERALD J. FRIEDMAN, M.D., (*New York*): The importance of this subject is borne out by the high incidence of deaths due to coronary artery disease in diabetes, the extent of coronary atherosclerosis in diabetes in general, and the increased incidence of coronary artery disease in diabetics as compared with nondiabetics under forty years of age.

In discussing the clinical features of myocardial infarction in the diabetic, Dr. Marble showed the difficulties of making the diagnosis of diabetes in a patient with myocardial infarction. I should like to reverse the problem and stress the difficulties, and importance, of making a diagnosis of myocardial infarction in a patient with diabetes. The presence of chest pain, nausea, vomiting, shock, hyperglycemia and ketosis in a patient with diabetes may suggest a diagnosis of impending coma, whereas the presence of a myocardial infarction may be overlooked. The association of acute coronary occlusion with diabetes requires extreme caution in treatment. The overenthusiastic administration of insulin could enhance the myocardial disturbance already present. The vigorous administration of fluids, especially saline, could over-

load the damaged heart and induce congestive failure. The correction of shock, dehydration, and ketosis is essential, but continuous, close clinical observation and chemical study must be maintained.

Under the heading of treatment of coronary artery disease in the diabetic, Dr. Marble mentioned the disagreement which exists concerning the use of anticoagulants. In his practice, anticoagulants are used only for those patients who are most acutely ill, who have suffered the most severe degrees of infarction, who are much overweight, or who have had a past history of thromboembolic episodes. However, I feel that diabetes in itself is an indication for the use of anticoagulant therapy in myocardial infarction. As pointed out by Anderson, the vascular degeneration in diabetes is tridimensional, attacking the arteries (and arterioles), veins, and capillaries. Warren showed that phlebosclerosis is a not infrequent finding in legs amputated for diabetic gangrene. In addition, hemoconcentration, which favors the development of thrombosis, is a frequent concomitant of uncontrolled diabetes. A major reason for the use of anticoagulants is the prevention of peripheral vessel thrombosis. Therefore, in the absence of a specific contraindication such as a bleeding tendency, diabetics with myocardial infarction should receive the benefit of treatment with an anticoagulant.

In conclusion I should like to discuss the prognosis of coronary occlusion in the diabetic. Dr. Marble mentioned that diabetic patients with heart disease generally have a poorer prognosis than nondiabetics. The most important factor in the prognosis is the degree of control and the presence of ketosis. Mintz and Katz, in their excellent monograph on myocardial infarction, reported that of eighty-five patients with myocardial infarction and diabetes, nineteen (22.4 per cent) had ketosis on admission to the hospital, and ten of the nineteen died. Twenty-five others (29.4 per cent) were in a poorly controlled diabetic state (the urine contained 3 to 4 plus sugar). When the number of patients with uncontrolled diabetes and those with ketosis was subtracted from the total number of diabetics, the mortality percentage of the remainder was about the same as that of the nondiabetics. Diabetes definitely increases the mortality rate, primarily by leading to an uncontrolled diabetic state after infarction.

Much remains to be learned about the cause of the high incidence of this so-called complication of diabetes, but the findings reported today reveal the progress that is being made.

IRVING GRAEF, M.D., (*New York*): Dr. Marble, have you any data on the frequency of heart failure in normotensive diabetics with evidences of coronary disease? I ask this because I have been struck several times in the last few years with the occurrence of left ventricular failure in acute episode in normotensive diabetes. Several patients had mild diabetes, and in two it was severe.

The question of cardiopathy was a source of trouble to us clinically. The hearts are usually normal in size, certainly as judged by roentgenograms, and in three cases, which came to nephropathy, the hearts were normal in size.

Have you any data on the association of myocardial infarction with diabetic retinopathy as a possible clue to the coexistence or the separation of these two types of vascular lesions? If, as the discussion has indicated, the medium-size vessel is subject to one kind of atherosclerosis and the capillaries to another, this may be a way for us to separate the two in studies such as yours.

DR. MARBLE, (*concluding*): We have from time to time encountered heart failure in normotensive diabetic patients with coronary heart disease. However, no exact data are available as to the frequency of such. Of the 102 patients in the series of Bradley and Bryfogle, nineteen gave a history of congestive heart failure prior to the time of the acute myocardial infarction; of these, ten had had hypertension and nine had not. Seventeen of the nineteen patients died within sixty days.

Many diabetic patients with myocardial infarction have diabetic retinopathy of varying degree. In younger patients, retinopathy has commonly preceded clinical evidences of coronary disease. In older patients, the reverse has been true, possibly because of nondiabetic influences which have contributed to coronary disease. However, in the diabetic both retinal and coronary involvement has seemed part of a generalized vascular damage related to inadequately controlled diabetes over a long period of time.

SUMMARIO IN INTERLINGUA

Morbo del Arteria Coronari in Diabeticos

1. Morbo del arteria coronari es mesmo plus frequente in diabeticos que in individuos nondiabetic. Illo causa quasi 50 pro cento del mortes in casos de patientes con diabete.

2. Inter patientes de plus juvene gruppos de etate le frequentia e le severitate de morbo del arteria coronari es plus alte in diabeticos que in nondiabeticos.

3. Inter diabeticos, morbo del arteria coronari occurre tanto communmente in feminas como in homines. Isto contrasta acutemente con le situation in nondiabeticos pro qui le morbo monstra un frequentia tres o

quatro vices plus alte inter homines que inter feminas.

4. Ben que hypoglycemia debe esser evitate in patientes con morbo del arteria coronari, on non pote eliminar le tractamento a insulina in casos de diabete. In loco de isto on debe prescriber un exacte dieta therapeutic e combinar lo con administrationes de insulina, precisemente como in le casos de omne altere patientes diabetic. Cetosis pote initiar infarcimento myocardial in patientes qui es predisponite a un tal disveloppamento a causa del presentia de morbo del arteria coronari in forma avantiate.

5. Pro le diabetico con morbo del arteria coronari le prognose es multo minus favorabile que pro le non-diabetico con ille morbo. Inter 1943 e 1948 un total de 102 tal patientes con acute infarcimento myocardial esseva admittite al New England Deaconess Hospital, e 60 pro cento de illes moriva intra le prime duo menses. Le prognose esseva pejor in patientes de etates plus avantiate, in femininas, in patientes hypertensive e obese, e in casos con previe historias de angina de pectore, infarcimento myocardial, o congestive dysfunctionamento cardiac.

6. Le prevention o retardation del disveloppamento de morbo del arteria coronari depende (1) del protection contra excessos de peso, effectuate per le restriction del contento de grassia e del contento caloric del dieta, e (2) del caute e continue surveliantia del condition diabetic.

Water and Salt Metabolism in Diabetes

The disturbances of water and salt balances in diabetes are of four kinds: (1) the diuresis of profuse glycosuria; (2) the edema of malnutrition; (3) the phenomena of diabetic acidosis; and (4) complications arising from associated vascular and renal disease especially the Kimmelsteil-Wilson syndrome.

When the plasma sugar rises above a certain concentration the quantity of glucose presented to the tubules by the glomerular filtrate exceeds their reabsorptive capacity. The sugar that thereby escapes reabsorption limits reabsorption of water in the terminal tubules. In addition, the glucose which accumulates in the extracellular fluid, being unable to penetrate cells freely, increases the effective osmotic pressure of this fluid. This draws water from the tissue cells, inhibits the reabsorption of sodium chloride from the tubules and provokes thirst. The net result is polydipsia, polyuria, dehydration and salt depletion. The degree of the last two depends on the supply of salt and water and the magnitude and continuity of the hyperglycemia. The patient taking an adequate diet and water as desired may excrete as much as 150 gm. of glucose daily without evidence of wastage of salt or reduction of serum sodium, presumably because the supply of salt is adequate and because immoderate hyperglycemia does not persist throughout the twenty-four hours. Such patients are probably always somewhat dehydrated, especially in the morning, which also tends to sustain the concentration of sodium in the serum. Elimination of glycosuria almost invariably results in an immediate slight, persistent increase of body weight. The proper treatment of the polyuria consists in the elimination or reduction of the glycosuria by a proper regulation of the diet and, when necessary, administration of insulin. Whether glycosuria *per se* is deleterious is open to argument; when it reaches symptomatic proportions, argument ceases.

If diabetes becomes sufficiently grave to interfere with nutrition serum albumin falls and edema appears. While glycosuria persists its diuretic effect may be great enough to keep the edema in abeyance. The edema is most likely to make its appearance when diabetes is first brought under control. Like other nutritional edemas it is aggravated by salt and responds to salt restriction and diuretics. In most instances it requires no specific treatment because it disappears spontaneously as malnutrition is overcome. Occasionally, when it has assumed embarrassing proportions salt restriction, and possibly, administration of urea are justified. Patients with malnutrition sometimes manifest an inexplicable craving for salt which provokes or aggravates edema. Restraint of this craving may be enough in these cases to prevent or eliminate the edema. After recovery from acidosis, edema may appear without demonstrable hypoproteinemia. The cause of this edema is not entirely clear. It has been suggested that it owes its origin to a slight bicarbonate excess and alkalosis with which it is usually associated. This heightens rather than solves the mystery because the alkalosis itself requires explanation.

From the book *Diseases of Metabolism* edited by Garfield G. Duncan, M.D., Philadelphia, W. B. Saunders Co., 3rd ed., 1952, Section on water balance in health and disease by John P. Peters, M.D., pp. 412-13.

Prevention of Vascular Disease in the Diabetic

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In view of the present state of our knowledge, the title of this paper is ambitious. I may begin with the unequivocal statement that neither my associates nor I have any magic formula which predictably will prevent vascular disease in the diabetic. However, I should like to consider with you some of the observations of others, and some observations of our own which bear upon this subject.

In our own thinking, diabetes mellitus is divided into two diseases: the form that occurs typically in middle age, which, from a functional standpoint, we consider as presenting essentially a problem in hypoinsulinism with associated metabolic abnormalities; and juvenile diabetes, which represents a combined problem of hyperpituitarism and hypoinsulinism.

In both groups one deals with two vascular problems. One, atherosclerosis, is identical with that which afflicts the average nondiabetic member of the American population, if he lives sufficiently long. Statistically, the onset of this vascular disease in the diabetic is earlier and the progress more rapid. The other is a rather specific disease, in which characteristic changes occur in the retinal and glomerular capillaries. This latter problem is most distressing in the juvenile diabetic, because of its occurrence at an early age.

ATHEROSCLEROSIS IN ASSOCIATION WITH DIABETES

With the possible exception of cancer, no field of clinical investigation is receiving more attention than that of degenerative vascular disease. Since atherosclerosis in the diabetic appears earlier and progresses more rapidly than in the nondiabetic, and since we have some knowledge of the endocrine and metabolic abnormalities which occur in diabetes and which, at least in part, are presumably related to the pathogenesis of the vascular disease, it seems logical to conclude that the answer to the over-all problem of atherosclerosis might very well be found more readily in the diabetic than in the nondiabetic population.

This is not the occasion for discussing all the divergent concepts regarding pathogenesis and management of atherosclerosis. Essentially there are three major points of view:

1. that dietary cholesterol is the most important factor in the production of atherosclerosis;

2. that dietary cholesterol is relatively unimportant, but that some disturbance in cholesterol metabolism is nonetheless the major abnormality in individuals who develop atherosclerosis;

3. that disorders of lipid metabolism are secondary, and that disorders of protein and/or other nonlipid metabolism are primary. There is disagreement as to the importance of nutritional factors among those who adhere to this concept.

It may be stated categorically that no individual or group knows the answer to the pathogenesis, the laboratory diagnosis, or the precise clinical management of atherosclerosis. If this is correct, does one have any reason to believe that there are available empirical procedures which, if adhered to, will lessen the incidence and/or the rate of progression of atherosclerosis in the diabetic subject? I believe the answer is a definite yes.

DIABETIC RETINOPATHY AND NEPHROPATHY

Kimmelsteil and Wilson[1] in 1936 described the intercapillary lesions in glomeruli of diabetic patients. Seven years later Ballantyne and Loewenstein[2, 3] described the retinal capillary aneurysms in similar individuals. Since these reports appeared there has been increasing acceptance of the essential identity of the pathology in both these organs.[4, 5] Aneurysmal dilation of capillaries has been seen in affected glomeruli, and no difference has been shown histochemically in the staining characteristics of the nodules in the kidneys and the hyalinized capillary aneurysms in the retinas.[6] This form of vascular disease may occur in the middle-aged diabetic, but it occurs most characteristically in the juvenile diabetic. Its recognition and the emphasis which it has received in the last decade are largely due to the survival of juvenile diabetics, who without insulin and antibiotics would not have lived sufficiently long to develop any form of vascular disease.

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RELATION OF CONTROL OF DIABETES TO THE DEVELOPMENT OF VASCULAR DISEASE

It is generally recognized that two major schools of thought exist in regard to management of the diabetic patient. The first is committed to the proposition that a goal of diabetic management is the maintenance at all times of a blood sugar within a normal range. The second school believes that the psychologic wear and tear attendant upon the maintenance of a physiologic norm in regard to blood sugar is not justified by the results achieved, and pays homage to something which is loosely called a "free diet."

One might fervently wish that the latter concept were correct, but it is only necessary to examine the literature objectively to be certain that it is not. In support of this statement are the numerous publications based upon the extensive experience of members of the Joslin Clinic.[7-9] Their experience and concepts are supported by many other careful observers. The situation is well summarized by Engleson[10] in a recent monograph. Specifically, a recent report by Dunlop[11] recounts "the straying from the straight and narrow path" of this investigator for a period of years, followed by a return to the principles of physiologic management. From his statistics and others like them, it is obvious that the incidence of complications is inversely proportional to the adequacy of control. The complications which are included are retinopathy, nephropathy, cardiovascular complications, tuberculosis and neuropathy.

If one accepts, then, the statement that good diabetic control results in a much lower incidence of vascular complications than "free" diabetic management, in terms both of time of onset and of rate of progression, a number of questions arise, among which are the following:

1. Can vascular disease be completely prevented in the diabetic by a program of optimal diabetic control? Is optimal control possible in all diabetics?

2. What are the quantitative and qualitative factors which enter into optimal control?

3. If a "free diet" is synonymous with relatively early onset and rapid progression of vascular disease, what are the known or probable factors which bring about such a relationship?

On the basis of my experience and that recorded by others, one may say that increased incidence of vascular disease in the relatively benign diabetes of middle age can be prevented by optimal diabetic control, in terms of our present conception of the term. Insofar as juvenile diabetes is concerned, Joslin's "Quarter-Century Victory Medal" patients indicate that the onset of vascular disease in such patients may be postponed for a long period. Dr. Joslin[12] has written us that as of mid-September 1954 the patients who have received the medal numbered fifty-four. In our experience, however, there are a certain number of juvenile diabetics whose disease is so severe as to make excellent or even good control a clinical impossibility. Representative of this is the blood sugar chart of a patient followed on the metabolic ward for a prolonged period of time (figure 1). This patient, even under conditions of chemically constant dietary intake, required insulin every six hours or oftener in order to maintain a blood sugar level within the normal range.

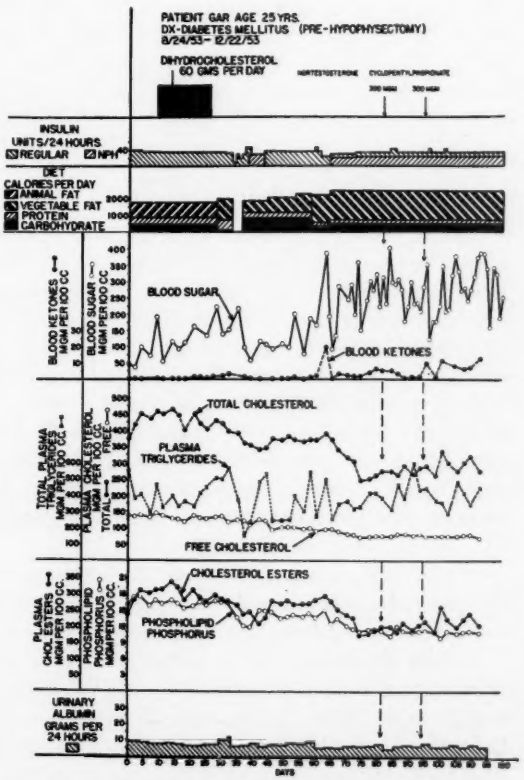

FIG. 1. Only the administration of "regular" insulin every six hours resulted in maintenance of normal blood sugar levels in this severe diabetic.

One must approach the answer to the second question most cautiously. Obviously the maintenance of a normal blood sugar is not the only essential criterion, since it is theoretically and clinically possible to maintain such control in many diabetics on diets grossly deficient in

protein, electrolytes, and/or vitamins. In the light of our present knowledge (or ignorance), perhaps the following definition will do: a diet containing protein adequate in amount and in biologic quality to permit of normal growth and repair; sufficient carbohydrate and fat to produce an optimal weight-height relationship, and thereafter to maintain caloric equilibrium; a qualitative and quantitative balance between insulin and carbohydrate to permit of maintenance of a true blood sugar between 60 and 160 mg. per 100 cc. throughout the twenty-four hours; sufficient carbohydrate combustion to prevent hyperketonemia; and an intake of essential vitamins, unsaturated fatty acids, and minerals sufficient to provide for growth and repair of all tissues.

Because of the almost hysterical emphasis upon the dangers of dietary fat and cholesterol in recent medical and lay literature, there has been a tendency to curtail dietary fat intake in diabetics, with a consequent increase in concentrated carbohydrates. Such a program makes for maximal fluctuations in blood sugar, particularly if a single-dose insulin regimen is utilized. A report by Johnson and Rynearson[13] of the Mayo Clinic makes untenable the concept of a mandatory relationship between atherosclerosis and high fat-high cholesterol intake. The patient referred to in this report had for twenty-nine years adhered rigidly to a diet containing 254 gm. of fat, 50 gm. of protein, and 46 gm. of carbohydrate. His blood pressure and ophthalmoscopic and neurologic findings were normal. There was no clinical evidence of peripheral vascular disease. The blood lipids were normal, and the urine examination revealed no abnormality.

The answers to the third question must for the present remain purely conjectural. Our own working hypothesis is as follows:

1. The most important abnormality which causes diabetics to be more susceptible to vascular disease than nondiabetics is broad fluctuation in blood sugar levels.

2. Such fluctuations over a period of months and years, because of disturbed intracellular and extracellular osmotic relationships, bring about functional abnormalities and finally structural cellular change. Prominent among such changes are those in the vascular intima.

3. Damage to endothelium having occurred, abnormal deposition of lipids and other material occurs in the damaged cells. Any factors, endogenous or exogenous, which tend to produce an elevation of plasma cholesterol will probably aid this process.

SPECIFIC DIETARY FACTORS

For present purposes, I shall dismiss the important aspect of vitamins in relation to diabetes and diabetic vascular disease with the statement that the problem is complex. In addition to using diets which are well balanced, our own approach is, in adult patients to provide vitamin supplementation insofar as the B complex group of vitamins is concerned, and in growing children to provide in addition supplementation with the fat-soluble vitamins.

Protein. Dietary protein has frequently received rather offhand treatment in the calculation of diabetic diets. A magical figure of "one gram of protein per kilogram of body weight" seems to be firmly implanted in the minds of most physicians. Assuming that the protein is of good biologic quality, this is a perfectly adequate figure for an adult diabetic whose disease is well controlled, that is, who is not wasting sugar, and whose diet is adequate in other respects. It may not be adequate for a poorly controlled adult diabetic, and most emphatically is not adequate for any diabetic who is still in a period of active growth.

Carbohydrate. If a major part of optimal diabetic management is the maintenance of a blood sugar within a normal range, and if one attempts to maintain most of his patients on one, or at the most two, doses of insulin daily, it follows that concentrated carbohydrate must be used sparingly or not at all. In other words, essentially all of the dietary carbohydrate must be derived from sources containing less than 15 per cent of carbohydrate. This in turn means a diet which is potentially unpleasantly bulky. Consequently, the total dietary carbohydrate will rarely exceed 160 gm. per day, and a considerable portion of the caloric requirement must be obtained from fat.

Fat. The metabolism of lipids is less well understood than that of either protein or carbohydrate. Because of the finding of lipid deposits in vascular lesions, dietary fat has been viewed with alarm. The case report cited by Johnson and Rynearson[13] is, therefore, reassuring.

Until recently the source of fat was considered to be of little importance insofar as relationship to blood lipid content was concerned. Observations from our own laboratory during the past few years, however, indicate that the source of dietary fat is of major importance in this regard.[14–19] Specifically, the administration of large amounts of vegetable fat, with complete exclusion of animal fats in the diet, has resulted in a striking decrease in the level of cholesterol and phospholipids in the plasma in all individuals studied, regardless of whether their initial plasma lipids were high, normal, or low. In some juvenile diabetics with hypercholesterolemia in association with advanced vascular disease, including retinal disease, the decrease in plasma lipids

associated with such dietary intake has been associated with major subjective and objective improvement in the retinal condition. This statement is made cautiously, inasmuch as at least a portion of the clinical improvement may be attributable to better diabetic control in some of these patients. Representative of the changes in serum lipids which may be achieved with a high vegetable lipid regimen, in figure 2 are shown the changes in plasma lipids in one of our recently studied diabetic patients with marked hypercholesterolemia.

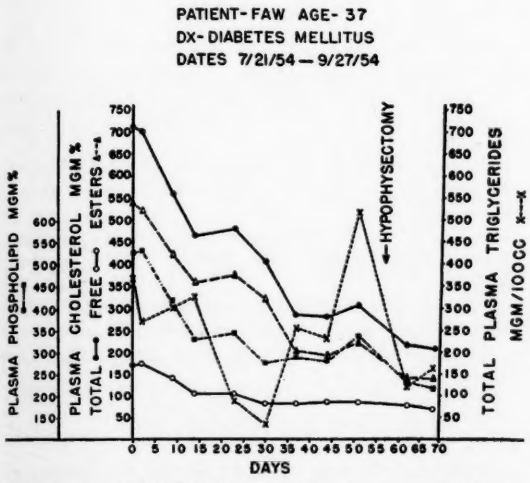

FIG. 2. A mixed diet high in vegetable fat, corrected hypercholesterolemia in this patient within a period of approximately one month.

The mechanism of the above effects is by no means clear. Conceivably the effect could be negative, that is, merely attributable to absence of cholesterol and related materials in the vegetable fat. Equally conceivably it could be positive, that is, attributable to some positive factor in the vegetable lipid which produced the changes in plasma cholesterol and phospholipid. In our hands to date, no fat derivative has produced changes of the constancy or of the magnitude noted with the high vegetable lipid diet. The same statement so far seems to apply to diets from which *all* lipids have been excluded.

In our clinic, diabetics are maintained on diets which contain from 100 to 150 gm. of protein (unless renal insufficiency is present), which are nearly or completely free of concentrated carbohydrate, and which consequently are high in fat. Except in patients with demonstrable vascular disease and/or hypercholesterolemia, the fat is of mixed vegetable and animal origin.

THE RELATIONSHIP OF ENDOCRINE FACTORS TO VASCULAR DISEASE IN THE DIABETIC

Directly or indirectly, the pituitary and the adrenal cortex appear to be implicated in diabetic retinopathy and nephropathy. Lukens and Dohan[20] reported renal lesions in a dog made diabetic by injections of anterior pituitary material. These lesions were similar to those described by Kimmelsteil and Wilson. Becker[21] noted no characteristic retinal or renal lesions in alloxan-diabetic rabbits, but was able to produce both when cortisone was administered. Corticotropin produced similar lesions. Rich, Berthrong and Bennett[22] reported glomerular nodules in nondiabetic rabbits receiving cortisone for three weeks.

Increased production of corticoids during pregnancy is only one small part of the increased endocrine activity which occurs, but whatever the reason, the aggravation of existing diabetic vascular disease during pregnancy is well documented, as well as its regression following the termination of pregnancy.[21, 23, 24] Retinal capillary aneurysms have been observed in nondiabetic and diabetic individuals during the administration of corticotropin.[25]

Conversely, improvement in diabetic retinopathy has been reported following bilateral adrenalectomy and following the superimposition of Sheehan's syndrome upon pre-existing diabetes.[26-28]

In our limited experience, unequivocal improvement in retinopathy and probable improvement in nephropathy appear to follow hypophysectomy in diabetic patients with advanced vascular disease.[29] Hypophysectomy invariably transforms a severe diabetes into a mild one.

Certainly neither adrenalectomy, hypophysectomy, nor any other form of surgery represents the final answer, even if it should prove to be a reasonably efficient answer, to the prevention of diabetic vascular disease.

EXERCISE IN RELATION TO DIABETIC CONTROL AND VASCULAR DISEASE

Assuming good diabetic management both at home and in camp, the insulin requirement of the average juvenile diabetic who goes to camp decreases by more than 40 per cent.[30] Factors other than exercise may play some part in this rather remarkable change, but it seems reasonable to assume that increased physical activity is the major factor which is responsible.

One of my friends, presently aged forty-seven, is a diabetic of twenty-nine years' duration. Having observed his habits in regard to the intake of food and drink over a period of some years, I would rate his diabetic control

as poor by any criteria. If one looked no further than this portion of his history, he could be pointed to triumphantly by proponents of the "free diet" philosophy, since prior to six months ago his vascular status was such as to qualify him for one of Dr. Joslin's victory medals. His program, year in and year out, includes strenuous tennis. One case proves nothing, but we suspect strongly that but for tennis this man's vascular status would be very different. If this assumption be correct, daily strenuous physical activity should be as much a part of the juvenile diabetic regimen as constant diet and insulin. Whether such a program can consistently counteract the deleterious effects of a "free diet," one may only guess at the present time. This question impresses us as well worth careful evaluation.

SUMMARY AND CONCLUSIONS

Vascular disease in the diabetic appears to be the resultant of exogenous and endogenous factors. For present purposes, it is probably permissible to oversimplify the problem and to arrive at a few conclusions.

1. The incidence of atherosclerosis is higher and the age of onset earlier in the diabetic than in the nondiabetic population.

2. Kimmelsteil-Wilson nephropathy and associated retinopathy appear to be essentially identical processes from a pathologic standpoint, and to be peculiar to diabetics.

3. Assuming a diet adequate in other respects, the maintenance of a blood sugar within a physiologic range will significantly decrease the incidence and severity of vascular disease in the diabetic. This is equivalent to stating that a "free diet" is unphysiologic and predisposes to vascular complications.

4. Because of the production, directly or indirectly, by the pituitary of excessive amounts of "anti-insulin factors," optimal control is clinically impossible in some diabetics. In patients in this category in whom vascular disease is progressing rapidly, hypophysectomy (and possibly adrenalectomy) may decelerate or halt the progress of the vascular disease. Conceivably, strenuous exercise begun early in the course of the diabetes, and taken regularly may have some prophylactic value.

5. The evidence is lacking that a high fat diet in a nonobese patient in itself predisposes to vascular disease. A case has been cited in which a diabetic was maintained on an ultra-high fat diet for twenty-nine years with no demonstrable vascular disease. In diabetics with vascular disease in association with hypercholesterolemia, the administration of a diet high in fat, exclusively of vegetable origin, will predictably result in a fall of cholesterol and other lipids to a normal range. Under these circumstances, such a diet may have therapeutic value.

ACKNOWLEDGMENT

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SUMMARIO E CONCLUSIONES IN INTERLINGUA

Prevention de Morbo Vascular in Diabeticos

Morbo vascular in diabeticos pare esser le resultante de factores exogene e endogene. In le presente contexto il es probabilemente permittite simplificar le problema e formular le sequente conclusiones:

1. Inter diabeticos, comparate con le population non-diabetic, le frequentia de atherosclerosis es plus alte e le declaration del morbo occurre a etates plus juvene.

2. Nephropathia de Kimmelsteil-Wilson e le retinopathia associate con illo pare esser processos identic in essentia ab le puncto de vista pathologic. Illos pare occurrer solmente in casos de diabete.

3. Providite que le dieta es adequate in altere respectos, le mantenentia del sucro sanguinee intra limites physiologic va servir a significativemente reducer le frequentia e severitate de morbo vascular in diabeticos. Iste assertion significa que un "dieta libere" es aphysiologic e predispone a complicationes vascular.

4. In certe patientes le glandula pituitari produce, directe- o indirectemente, quantitates excessive de "factores anti-insulinic." In tal casos le optime regulation del morbo es clinicamente impossibile. Si patientes de iste typo exhibi un rapide progresso del morbo vascular, le execution de hypophysectomia (e forsan de adrenalectomia) pote servir a decelerar le processo. Il es possibile que strenue exercitios, initiate promptemente in le curso del diabete e continuate regularmente, ha alicun valor prophylactic.

5. Il non existe datos a supportar le conception que, in patientes nonobese, dietas ric in grassia suffice a establir un predisposition a morbo vascular. Nos cita un caso in que un diabetico se manteneva super un dieta ultraric in grassia durante un periodo de 29 annos sin ulle demonstrabile signo de morbo vascular. In diabeticos con morbo vascular in association con hypercholesterolemia, le administration de un dieta ric in grassia de origine exclusivemente vegetal va resultar predicibilemente in un reduction del contento de cholesterol e de altere lipidos a valores normal. Sub tal conditiones, un dieta del typo mentionate pote esser de valor therapeutic.

Management of the Diabetic with Vascular Disease

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Vascular disease and its devastating end-results constitute one of the major problems faced by the medical profession today. The steadily increasing duration of life, with large numbers of the population living to sixty-five years of age and over, is bringing in an era in which degeneration of all systems must constitute a challenge. The diabetic too must pay the price of living longer by being more likely to develop degenerative disease and its complications.

The remarkable contributions in the field of vascular disease during the last three decades have added to the insight into these disorders. It is commonly considered that involvement of the vascular system is inevitable in the diabetic, provided he lives long enough. One does see, however, a few individuals with diabetes of many years' duration who seem to have escaped the ravages of time and have no demonstrable changes in their vascular tree.

That arteriosclerosis in diabetes increases with the duration of the disease is evidenced by the figures quoted by Root,[1] who noted that this process as a cause of death increased from 17 per cent at an average age of 44.5 to 70 per cent at an average age of 65.3.

As will be discussed below, diabetics seem to have a greater incidence of arteriosclerosis and atherosclerosis than does the general population. Although these conditions appear to differ in no respect from those found in nondiabetics, nevertheless, there is evidence that certain vascular changes, particularly in the retina and kidneys, may well be peculiar to the complicated metabolic disturbance found in diabetes mellitus. In many organs of the diabetic, vascular lesions are found with special frequency. They will be more fully described as the individual anatomic units are discussed. White,[2] who studied juvenile diabetics who had lived twenty years or more after developing the disease, noted some evidence of vascular disease in 92 per cent, an astounding figure.

Factors playing a role in this increasing incidence, such as an inheritance of a defective vascular tree, seem to have some influence. Nutrition in a broad sense, infection (which is notoriously more frequent in the diabetic), so-called toxic factors, hormone imbalance, and capillary fragility all may play a part, although one cannot justifiably accuse any one of these.

There has been much debate concerning the part that disturbances of lipid metabolism involving S_f10-20 and 20-100 lipoproteins and cholesterol may play in the various lesions in the blood vessels of the diabetic, but no convincing conclusions have yet been reached. There is, however, evidence that somewhere within this realm of changes there may be factors which have something to do with bringing about deviations from the normal in the vascular system. The role of brief, repeated disturbances in lipid metabolism, such as occur with acidosis, in initiating changes is not clear but is thought by some to be of importance.

Of particular interest is the work of Mendlowitz and his associates[3] who using the plethysmograph found that nine of thirty-eight diabetics, all under fifty and with diabetes for less than ten years, had blood flow readings in the hallucal circulation which were below normal limits, as compared with a similar control group of nondiabetics. Strikingly, none of these patients gave clinical evidence of vascular disease.

Somewhat similar results were obtained by Megibow and his co-workers.[4] Using a photoelectric recording method and a microplethysmograph, they examined forty-seven diabetics without clinical manifestations of vascular disease, twenty-seven of whom were females. Twenty-two had questionable peripheral vascular disease. After release of vasospasm, fifteen of these patients finally gave certain evidence of changes in the minute vessels of the extremities. These authors suggested an "occlusive angiopathy" of the smaller vascular radicles, which in turn might lead to increased resistance, thus accelerating arteriosclerosis.

These two reports suggest a method of detection of the earliest phases of vascular disease in diabetics and should prove most valuable in correlating early small vessel changes with disturbances known and unknown. Ditzel,[5] examining the vessels of the retina and conjunctiva, seems to find early changes peculiar to diabetes.

It should be emphasized that the duration of diabetes

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is agreed to be a fundamental factor in the production of changes in the blood vessels. With but few exceptions, patients who survive the longest have the most changes. Whether the various factors implicated in the control of the disease, such as diet, insulin, shock, and coma, are pertinent is subject to considerable debate. Most authorities believe that good control, with diet and insulin dosage adjusted to keep the blood sugar within reasonable normal levels most of the time, are of real significance in preventing these changes.

Recently a number of observations regarding control have been published. Keiding, Root and Marble,[6] reviewing a series of 451 patients—241 males and 210 females—observed that retinopathy, nephropathy, and calcification became increasingly prevalent as the degree of control worsened. Styron[7] followed 519 cases for one to six years and found that vascular complications increased with the duration of diabetes. Nineteen per cent had diabetes for twenty years or more without evidence of degenerative changes. On the other hand, no patient with diabetes of twenty years' duration and poor control was free of changes. None with good control had advanced retinal or renal lesions.

Dunlop[8] started with a group of fifty patients previously reported in 1951, all of whom had been treated with a "free diet" for five years. Seven of these had to revert to a controlled diet because of acidosis, etc., two had to do so because of frequent insulin reactions, and two became obese and had pruritus, necessitating a change in treatment. Of the remaining thirty-nine classed as satisfactory, only nine were considered to be so in 1954; three had become obese and had pruritus, nine had developed active tuberculosis, fourteen had developed retinopathy, and four had died from cardiovascular disease. Of 167 patients observed by him for fifteen to thirty-one years, freedom from vascular complications was four to five times as common in the well controlled patients as in the poorly controlled. Dunlop states that he has "returned to his previous diabetic faith," namely good control. The weight of evidence, in my opinion, favors the viewpoint contained in this and other studies.

Perhaps the most intriguing work being done in this field is that pertaining to the changes in the eye and kidney. Mackenzie, quoted by Ditzel,[5] first called attention in 1877 to the presence of capillary aneurysms in the eyegrounds in diabetics. Only passing attention was paid to these changes in the ensuing years, and it was not until recently that they were emphasized as one of the early lesions in diabetes mellitus.

Dana[9] reports that 90 per cent of his patients had retinal aneurysms, often associated with the Kimmelsteil-Wilson syndrome. Although these changes may occasionally be found in nondiabetics this still remains a characteristic finding. The fact that retinopathy is often associated with the Kimmelsteil-Wilson syndrome and that pregnancy and infection, both accompanied by increased adrenal cortical activity, may initiate or adversely influence the lesions, led Becker and his co-workers[10] to suspect that the adrenals were concerned. Urinary oxysteroids were found to be increased in diabetic retinopathy, and adrenalectomy sometimes resulted in betterment of retinal lesions. The administration of cortisone to rabbits has induced Kimmelsteil-Wilson-like lesions together with capillary aneurysms. These were also produced frequently in alloxan-diabetic rabbits. These same investigators state that patients with retinopathy excreted an increased amount of vitamin B_{12}. Lack of B_{12} supplement in the diet of these rabbits increased the frequency of the kidney lesions to 100 per cent. Just what part this vitamin plays in the picture, if any, is unknown at present. Neither B_{12} nor cortisone has proved of any value in the treatment of retinal and renal lesions in the rabbit or human being. It is fascinating to speculate on the possible implications of this important work, which indicates that retinal lesions and the Kimmelsteil-Wilson syndrome have much in common metabolically and pathologically. This suggests that these two lesions are part and parcel of the diabetic syndrome.

Unfortunately, control has relatively little to offer in the arrest of these lesions. One patient with retinopathy in whom necrosis of the pituitary (Sheehan's syndrome) occurred had regression of the lesions, and several patients with severe retinopathy had bilateral adrenalectomy with reported improvement. Dana, Eversole and Zubrod[11] state that over 50 per cent of their patients with the Kimmelsteil-Wilson syndrome had a progressive decrease in insulin requirement, some even becoming hypoglycemic. It should be pointed out that those with Kimmelsteil-Wilson lesions in the kidney often had an increased renal threshold. Derangements in the serum polysaccharides and mucoproteins have been noted in diabetics, suggesting that these may play a role.

The part played by infection in precipitating severe renal damage in diabetes is well known. This can lead to vascular changes, so that prevention, control, and investigation of urinary tract infections are of major importance in preventing severe renal damage. Good control seems to be a factor in patients with diabetes of long standing. Renal disease is one hundred times as frequent in diabetics as in nondiabetics according to Bell.[12]

The aging process in the diabetic carries with it vascular damage involving the coronary circulation, 4

per cent of all deaths from coronary disease being associated with diabetes mellitus in males and 14 per cent in females.[13] Coronary sclerosis was noted by Liebow and Hellerstein[14] in 74 per cent of autopsies done on diabetics. The preponderance of females was especially evident in this as well as the cardiovascular accident group. In both instances these lesions were much more frequent in the older diabetics, occurring two to three times as often as in nondiabetics—twice as frequently in males and three times as frequently in females. Feldman[15] reports that 43.8 per cent of diabetics had coronary disease at autopsy as compared with 20.1 per cent of nondiabetics. Renal damage was one hundred times as frequent in the diabetics.

Treatment of cardiovascular disease in the diabetic does not differ materially from that in the nondiabetic. Reduction of weight in the obese, relief from stress and strain, control of hypertension by newer methods of treatment, and freedom from acidosis may all be important. No finally proved effect can as yet be definitely attributed to the low-cholesterol diet. Insulin must be used with especial care in these individuals, for shock, with resultant increased cardiac output and greater strain on the heart, may precipitate an infarction. It is better in patients with demonstrable coronary disease to permit blood sugars slightly above normal than to try to achieve "knife-edge" control.

Infarction of the heart presents no problems in the diabetic not present in the nondiabetic except for care with insulin administration.

In the older diabetic dangerous complications are prone to occur as the result of changes in the peripheral circulation, more particularly in the feet. Fifty-one per cent of 249 male diabetics had evidences of clinical peripheral arteriosclerosis.[16]

Diabetics at any age should be examined carefully for evidence of reduced blood flow by the usual methods, namely routine palpation of the vessels of the extremities and search for color changes in the feet. Epidermophytosis, and minute infections should be noted since they may contribute to disease in the extremities. Every diabetic should be trained to give close attention to the feet, since this may prevent or delay serious and devastating lesions.

When evidence of impaired circulation in the lower extremities is present, careful evaluation must be made. A history of pain in the legs on walking (intermittent claudication) and in the more severe cases, pain when resting are important. Color changes are of value in estimating the degree of small-vessel involvement. Oscillometric observations may be useful in determining the extent of involvement. Recently arteriography has proved of distinct value in a few cases.

Treatment resolves itself into medical and surgical therapy. Prompt treatment of infection with the proper antibiotics is all-important, selecting the agent by testing organisms for specific sensitivity. Tobacco, because of its tendency to cause vasospasm, should be interdicted. Mufson[17] has recently advocated the use of histamine, given in the femoral artery in weekly doses combined with aureomycin and penicillin, if there is infection. He noted good results including relief of pain in the majority of his patients. Pote[18] has treated surface ulcers associated with gangrene by using a trypsin preparation (Tryptar) with Sorensen's buffer solution. He reported excellent results in most cases, including closure of draining sinuses.

McCarty[19] advocates Varidase (streptokinase-streptodornase) in the treatment of chronic infections, using soaks and foot baths containing the solution. This method was successful in conjunction with antibiotics in eighteen out of twenty-five of his cases.

Vasodilator drugs have been used widely. Priscoline in 25 to 50 mg. doses, four times daily, has been used with varying success. It has also been given intra-arterially, but severe complications have been reported. Nicotinic acid and Roniacol (the alcohol of nicotinic acid) have given good results. Dibenzyline also has been tried. My own experience with these agents has been disappointing and not at all consistent.

Sympathectomy has a definite place in therapy, even though there is no palpable pulsation in the posterior tibial or dorsalis pedal arteries, and superficial ulceration is present. Is is better, however, to employ this method before this stage is reached in order to achieve optimum results.

Surgery must finally be resorted to in many cases. Frequently transmetatarsal amputation suffices especially if some of the agents cited above are used in conjunction with it. The final selection of operation must be made by careful evaluation, best done by close collaboration between the physician and the surgeon. Arteriograms may help in the cases with unusual location of pain, suggesting involvement of the larger vessels, for instance common iliacs. With modern vascular surgery, more daring procedures are being carried out, with resultant benefit to the patient with peripheral vascular disease.

SUMMARY

Vascular disease is commoner in diabetics than in nondiabetics. Although a type common to both groups

occurs, there are changes in the small vessels which may be peculiar to the disturbed metabolism found in diabetes.

Management of several organ and system disorders is discussed.

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SUMMARIO IN INTERLINGUA

Tractamento de Diabeticos con Morbo Vascular

Morbo vascular es plus frequente in diabeticos que in nondiabeticos. Ben que il existe un typo de morbo vascular que occurre in patientes con e sin diabete, il ha etiam alterationes del parve vasos sanguinee que pare esser effectos specific del disturbate metabolismo que es associate con diabete.

Es discutite le tractamento de varie disordines de organos e systemas.

DISCUSSION

EDWARD TOLSTOI, M.D., (*New York*): Drs. Kinsell and Mulholland agree that vascular disease is more prevalent among diabetics than among nondiabetics. They agree that retinopathy and the Kimmelsteil-Wilson type of nephropathy are peculiar principally to the diabetic. They also agree that the precise cause or causes of vascular disease in diabetics are unknown. With these three postulates, I thoroughly agree. True, each presents hypotheses concerning vascular disease, and we hear such vagaries as hormonal imbalance. I do not know what that means. It can mean almost anything, and it can mean nothing. I should like more specificity.

Dr. Kinsell leans on the physiochemical hypothesis of atherosclerosis. Now, both speakers are uncertain as to the causes of atherosclerosis—they freely admit they do not know, and Dr. Marble hinted at that too. He does not know; he not only hinted, I think he admitted it—yet each one states that if you keep the blood sugar normal, you will reduce the incidence of these vascular complications. Dr. Kinsell stated that if the diet is adequate and you keep the blood sugar normal, everything will be fine, but the so-called "free diet" disposes to vascular complications.

With this concept I must disagree, not because I want to be contentious, but because there is no evidence for the statement. I hope to bring forth some evidence to support my point of view, and I hope to do it as ably as Drs. Kinsell and Mulholland presented their philosophy and evidence, based on their experience and data derived from the literature. I hoped they would present their personal results based on fifteen years of study: X number of cases and how many cases developed vascular disease on a diabetic regimen which they considered controlled.

Both speakers presented studies by the Joslin group,

Styron, Dunlop, and Engelson, all of which purported to show that the better the control—namely, the more normal the blood sugar over the twenty-four-hour period—the fewer the vascular complications; and of course the normal diet or what they call the "free diet" is condemned. Now, there is nothing "free" about the diet. It is a normal diet selected by the patient to suit his tastes, customs, and appetite. It is not weighed, nor is it measured. He sits at the table with others and partakes of the usual normal meal to satisfy his appetite. With this meal he may partake of desserts. That briefly is the normal diet, and differs little from your food habits or mine. It does not mean that because he is permitted a normal diet he is to consume tremendous quantities of food with prodigious amounts of sweets. Sufficient insulin in one daily dose is given to eliminate the symptoms of diabetes and ketosis and avoid hypoglycemia. Furthermore, the maintenance of the optimum weight is a must. On this regimen there is bound to be both hyperglycemia and glycosuria, both of which are asymptomatic, and I have seen patients excrete large amounts of glucose with normal urinary volume and no symptoms whatever. This resulting hyperglycemia, say Drs. Kinsell and Mulholland, is a factor, perhaps not the only one, in the causation of vascular lesions. Therefore, if we attempt to keep the blood to as normal levels as is practical—for most authorities admit ideal control is a wish and not a reality—shall we avoid or postpone the late complications?

In his paper which Dr. Mulholland sent to me, he quoted White and Waskow's series of 200 patients, twenty-year diabetics. The incidence of complications of vascular disease there was 92 per cent. I know it has been said that those cases were poorly treated, but I must disagree with that statement, because I do not know of any one who treats diabetes any better than the Joslin group. They have been setting the pattern for treatment for the entire world. This is something that has happened, and is happening in most diabetics irrespective of the type of therapy. It is a fact; the explanation for it may be that those patients were not treated well. I do not know. However, I certainly respect the type of therapy that has been established, and I followed for years their tenets and their teachings prior to my change in point of view. Dr. Joslin's book has always been my bible, so I cannot quite accept the idea that these cases were not treated very well. Their diets were carefully prepared and the rest of their care was in keeping with the high standards set for the world by Dr. White and her associates, and yet the incidence of vascular disease among those cases was staggering.

Fanconi, not mentioned by either speaker, also had disastrous results treating his diabetics by the orthodox methods. Here the apology was that the diets were inadequate in proteins.

The work of Jackson, from Iowa, is most impressive, and yet neither speaker chose to discuss his results. This is probably the most accurate and carefully controlled study on the relationship of chemical and dietary control and the development of vascular lesions. There were seventy-five children who had diabetes ten or more years. The diets were adequate judged by accepted standards. The patients were given three and at times four doses of insulin daily. They were hospitalized for long periods, and the parents were instructed in home care. Daily records were kept, and on follow-up visits the most exhaustive studies were made.

This was truly a most meticulous attempt to have the child's status as normal as possible, yet 46 per cent had retinopathy, 4 per cent hypertension, and 4 per cent nephropathy. Furthermore, Lundbaek found retinopathy in 67 per cent of "good controls" and 85 per cent of poor ones—not an impressive difference. These data, it seems to me, do not support the thesis that the more normal the blood sugar, the fewer the complications.

You have heard of differences of opinion not being limited to our country, but also prevalent in England. We have Dunlop and Matthews on one side—and incidentally, Dunlop's work needs a little careful analysis. In his study of the fifty cases, he said that seven of his cases developed decreased glucose tolerance. In other words, they needed more than 80 units of insulin a day, and therefore that disqualified them. Two cases developed obesity and pruritus, and that disqualified those cases. Two cases had insulin reactions, and that disqualified those cases. I do not think that is a fair assumption in those cases, because if they need more insulin, give it to them, and if patients have insulin reaction, we usually reduce the insulin and increase the food intake. Then, he had fourteen cases of retinopathy, which was 28 per cent. That compares with other technics. I cannot quite understand his figure of nine cases of tuberculosis—14 per cent. That is a staggering figure. It may have something to do with the type of diet that was prevalent in England at that time. Therefore, I do not think we need to get terribly excited about that. Goodby and Jacobs presented 602 cases from the St. Thomas Clinic—in the report published in 1950—and they concluded from these 602 cases that the type of control of diabetes is without effect on the incidence of long-term complications.

My own experience, to date, has certainly strengthened, and not shaken, my point of view. I personally followed forty-four diabetics (and as the years go by, that number increases) from ten to thirteen years. Every patient was examined by no one but myself. I did their urinalyses; I checked their blood pressure; I examined their eyegrounds. I did not do a single blood sugar determination during those entire ten years, on any one of those patients. Their urines always revealed a 2 to 4 plus glycosuria at each visit. Yet they lived normally, had no more upper-respiratory infections, worked, and certainly underwent major surgery. Of these forty-four patients, twelve showed a retinopathy, which is 28 per cent. This figure certainly compares favorably with the most rigid chemical technic. These data and nothing else cast doubts on the concept that a normal blood sugar will postpone vascular lesions. That the height of the blood sugar is the cause is a faulty premise, because the precise regulation of the blood sugar does not strike at the underlying metabolic defect any more than the reduction of the leucocyte count in leukemia alters the disease process.

Dr. Kinsell stated that the feeding of vegetable fats has been associated with subjective and objective improvement of retinal pathology. I have had no experience with vegetable fats, but I have seen a good many eyegrounds. Dr. Wise cautioned us against interpreting improvement as due to any specific therapeutic agent, because we have seen eyegrounds clear up whether the patient had glycosuria or had been aglycosuric. On the other hand, Dr. Mulholland stated that the control had little to do with the prevention of retinopathy.

In my series of forty-four patients already mentioned retinopathy was present in only twelve, or 28 per cent. As we go along, in the group from twenty to thirty-four years, with forty-three patients, twenty-two had retinopathy, and the others escaped. I have photographs of the eyegrounds of every one of those patients who escaped retinopathy. You can take my word for it, they have been checked by experienced ophthalmologists, and no retinopathy was there.

I want to thank both Drs. Kinsell and Mulholland for sending me their manuscripts, and for coming here and placing before us in sharp focus a problem about which we know very little. I do know that their data and discussions will stimulate us to further thought and search for what I hope is the proper answer.

BEVERLY CHEW SMITH, M. D., (*New York*): Being the only surgical discusser, I wish to avoid controversial statements. As a surgeon, I would rather treat a diabetic whose diabetes is controlled. The less controlled the patients are, the more frequently I like to see them, because I know from experience that they are closer to trouble than were they consistently controlled. The same hackneyed expression and word, with which our good friend Dr. Joslin is so familiar from a surgical standpoint, is prophylaxis. I cannot tell you how impressed I am with the laissez faire and lack of aggressive attitude that still exist amongst the general practitioners and some of those who treat diabetics exclusively. It is amazing to me to see the dirty feet of patients who have been treated by supposed diabetic specialists.

Concerning the use of vasodilating drugs, in my experience I have not been impressed by their efficacy. They have been used in clinics and in offices personally, and I have not been impressed by the clinical results. The side effects have to be watched. They are often dangerous. If one looks at the disease in the vessel wall under the microscope, it is hard to understand how such vessels could be dilated. About lumbar sympathectomy, I think the indications are being consistently narrowed, and as they are more narrowed, the results of this procedure will become more salutary.

The economics of the surgical side of this disease and its complications are important. Some fifteen years ago, at Presbyterian Hospital, I looked up the amount that the hospital billed 100 surgical diabetics and the amount they paid the hospital; the difference was about $150 per patient. That was during the time the ward rates were much cheaper than they are today. This is a tremendous problem for these people where prolonged hospitalization is usually necessary.

Concerning the use of antibiotics, I believe it is becoming an accepted practice to test each organism against various antibiotics and use only those which show the best individual response.

Lastly, a word about prophylaxis. It is prophylaxis and the care of patients' extremities with occlusive arterial disease that will prevent such a catastrophe as amputation—and amputations are catastrophes. In conclusion, should an amputation be necessary, it should be performed as low as possible. If you cannot amputate through the foot, amputate through the leg. I am most anxious to rid medical textbooks and the teaching in many medical schools over the country of the idea that a thigh amputation is the method of choice in these cases.

Since 1930, I have performed below-knee amputations in all cases except those in whom the disease extended to the knee joint or a pathologic knee joint precluded the use of a prosthesis. The great benefits of better ambulation and rehabilitation have, in my

opinion, justified the procedure. The percentage of reamputations has been about 2 per cent and the operative (including hospital) mortality about 10 per cent.

Amputees do not live long after amputation. In looking over amputations done in the past twenty years, one is struck by the small number who have survived for fifteen years. Only about four or five in this series have lived that long. Most of these patients die between five and seven years after amputation. If they have amputation through the thigh, they are nonambulatory, and somebody has to stay home to take care of them. The economic status is not only interrupted, but also they die earlier. Therefore, one should strive to preserve the knee joint.

ELAINE P. RALLI, M.D., (*New York*): In justice to Dr. Tolstoi's point of view, I think it is fair to state that the term "liberal carbohydrate diet" does not mean a diet extravagantly high in carbohydrate. We have used a fairly liberal carbohydrate diet in the clinics at Bellevue. The patients have done well, and the diet, which has been a reasonable one, has helped in the management of the patients.

It is obvious that all of us are agreed that we know very little of the pathogenesis of the degenerative lesions seen in the diabetic. These lesions seem to be commoner in patients with diabetes than in nondiabetics and occur in spite of good control of the diabetes. One thing that interested me in this discussion was the reference to the role of the pituitary gland and the adrenal cortex in the etiology of the degenerative lesions.[1] Although it is quite true that you can build up a convincing argument to support the idea, there are certain points that deserve discussion. For example, as a measure of adrenal cortical activity the excretion of the adrenal steroids has been widely used. However, the changes in methods for determining steroids have made it somewhat difficult to compare results from different laboratories, or in fact to know exactly what are the limits of the normal excretion of steroids. For example, in 1950, Thorn and his colleagues[2] reported the excretion of the 17-ketosteroids in a group of twenty-five normal males and twenty-five male diabetics. The average excretion of the diabetic males was 8.1 mg. per twenty-four hours as compared to 11.1 mg. for the normal male. In both groups the range was great.

In another study which Mason and associates[3] reported, insulin was withheld from a diabetic patient and measurements were done of urinary corticosteroid excretion, blood carbon dioxide content, and blood sugar for a period of fifty-four hours. During this time the excretion of the corticosteroids did not exceed normal levels. The eosinophil counts did not decrease until the second day. Mason has also confirmed these findings in a larger group of diabetic patients who were in acidosis. He found that the excretion of steroids only fell at the time when so many other changes were occurring that it was not possible to interpret the steroid changes as due solely to the diabetic ketosis.

Gray[4] at the University Hospital in London reported in 1953 on the excretion of steroids in normal females, normal pregnant females, diabetic pregnant females, and diabetic females who were not pregnant. There was no consistent difference in the pattern of excretion in the pregnant normal and pregnant diabetic patients.

The use of eosinophils as an index of adrenal cortical dysfunction is now acknowledged to be far from satisfactory. Thorn[2] reported in 1950 that he found fasting levels of eosinophils essentially the same in diabetic male subjects as compared to normals, and that he found the decrease in eosinophils occurring four hours after the injection of 25 mg. of corticotropin was slightly less in the diabetics than in the normals—65 as compared to 74 per cent.

One other point, which I did not hear mentioned, is of interest; that is the question of the functional activity of the thyroid gland in relation to the degenerative lesions. In a study we have just completed on over 300 diabetics, we found a rather significant incidence of hyperthyroidism. Fifteen per cent of the patients had hyperthyroidism. I cannot tell you, at the moment, how many had hyperthyroidism first and the diabetes later, but the two disturbances in metabolism did go hand in hand.

One particularly interesting case in this group was a young woman whom we have seen since the age of nine when she developed diabetes. She married, and when she became pregnant the first time, showed hypertension, albuminuria and increased insulin requirement. She was delivered normally, but the baby died during the delivery. She became pregnant a second time and, again, during the later part of her pregnancy required more insulin—this in spite of hormone therapy. She again developed hypertension and albuminuria. In the latter half of this pregnancy she also developed hyperthyroidism with an elevated basal metabolic rate. The hyperthyroidism was controlled with Lugol's solution. She was delivered of a normal baby by cesarian section. About a month after delivery she had a thyroidectomy. A year later she became pregnant again. This time she went through her pregnancy with absolutely no change in insulin requirement, no hypertension, and no albuminuria and had a completely uneventful delivery, again by

cesarian section.

The question as to the etiology of the vascular lesions presents one of the most fascinating problems in the disease. I should like to present some of our studies. Our premise has been that the action of a hormone may be influenced by the intracellular situation. This brings up the possibility that the basic metabolic defect in the human patient with diabetes is not primarily a lack of insulin, but rather an altered situation within the cell which modifies the effectiveness of insulin. The problem, of course, is to identify what cellular changes might exist which would condition the action of insulin. We have been doing studies on the bloods of normal and diabetic subjects of the same age and sex. The determinations have included studies of the albumin and globulin fractions of the serum by paper electrophoresis, measurements of the sulfhydryl content of the blood by amperometric titration, whole blood ascorbic acid and sugar, and serum cholesterol determinations. The sulfhydryl determinations were done because of the reported relation of these compounds to the blood sugar in experimental animals. The results have been somewhat disappointing. Plasma sulfhydryl in the patients with diabetes mellitus averaged slightly lower than in normal subjects. The difference was statistically significant. In the case of the nonprotein sulfhydryl groups (largely glutathione in the red blood cells) no significant difference was found between the normal and the diabetic subjects. The difference between the plasma sulfhydryl levels in the two groups of subjects studied is certainly slight but may possibly reflect some change in amino acid or protein metabolism in the diabetic patient. Another finding in the diabetic was an elevation of the alpha globulin levels.

One is not permitted to theorize too far on the basis of the evidence that we have. However, the question does arise as to whether there may not be a metabolic defect in the diabetic which precedes or accompanies the carbohydrate disturbance. This defect, which may be in protein synthesis, may be a factor in the later development of the vascular lesion. In the young diabetic the vehemence of the carbohydrate disturbance obscures any other metabolic changes. The cellular derangement, however, which later results in degeneration of the blood vessels, may already be present at this time.

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LAURANCE W. KINSELL, M.D., (*Oakland, California*): I should like to make one point that I did not make clear; that is, we do not feel for a moment that a high vegetable fat intake is a cure for anything. We would go along thoroughly with Dr. Tolstoi in the thought that one must attempt to interpret changes in fundi, either on the basis of appearance or function, with great caution. Thus, we present these data at this time only as data which indicate, first, that "fat is not fat," that is that vegetable fat and animal fat are two very different things insofar as the plasma lipids are concerned. Whether this means that a lower cholesterol which can be achieved by such a method is going to do anything good for atherosclerosis, or any other kind of vascular disease—years will elapse before anybody knows. The only thing we are sure of is that one can lower cholesterol by such means, and I think that certainly there is little reason to believe that an agent which will normalize plasma cholesterol will be harmful.

A reasonably high fat diet in a diabetic makes for better control than if one does not use a high fat diet—better control in terms of a blood sugar which can be kept in a range which is within the physiological norm.

The second comment, with particular reference to Dr. Jackson's statistics, is this: If one sets up any diabetic regimen which requires multiple doses of insulin a day, it means that one is giving insulin "by test," so to speak, and therefore one has presumably a blood sugar which is not staying in the physiologic range. If I had diabetes, I should prefer to run a consistently high blood sugar rather than have it way down one minute and way up the next. I should prefer still more to have it remain in a normal range. In support of this is a very simple experiment which anybody can do, with just a semipermeable membrane which has a manometer attached to it. If you put it in a beaker of water and let it achieve equilibrium, and then add or subtract different concentrations of glucose, the excursions in the manometer are impressively large.

I have a suspicion that cells do not take kindly to colloid-osmotic relationships where things are pulled out rapidly one minute, and pushed in rapidly the next.

I can think of no better way to make a cell misbehave, if one really wanted to.

HENRY B. MULHOLLAND, M.D., (*Charlottesville, Virginia*): I believe, Dr. Tolstoi, although Jackson did conclude that duration had the most to do with the development of vascular lesions, he did say that lack of control also was definitely related to their progression. I respect Dr. Tolstoi's opinions about this question, and maybe time will show that he has something.

I just do not happen to agree with him, but I am always interested to hear him talk about his views.

Types of Food Faddism

Food fads, and in this term I include also food quackery, may be considered in several categories. One type is the fad that arises merely as a fashion. I refer here to certain fads which have become well-established dietary customs and which, in themselves, are not necessarily pernicious, such as the drinking of tea and coffee. From a health viewpoint the possible disadvantage of such habits lies in the deprivation of benefits from products of better nutritional value, and conversely, in the use of non-nutritive substances when nourishment is needed.

A second type of food fad is that which attaches special virtues to a particular food or diet. Some apt examples are the various 'fruit cures' of the past and present. A typical fruit cure would tend to lower the intake of calories but raise the intake of certain vitamins.

Another fad of the special-virtue type is the distortion of the relative importance of vitamins and minerals. In the minds of many people, confusion seems to arise through failure to comprehend the basic nature of the vitamins as essential nutrients that do not in themselves produce energy or tissues, but without which neither energy nor tissue can be manufactured by the body. General understanding of the mediating roles of the vitamins in metabolism would do much toward resolving popular misconceptions about the relative merits of natural foods and synthetic vitamins.

A third category of food faddism is the belief that a particular food or class of food is harmful, either generally or to the individual. Fruits will again serve as an illustration. Several curious fallacies have prevailed regarding the tomato. In America it was long regarded as poisonous; and when first introduced into Europe, it was considered by some authorities to be aphrodisiac, and more recently, to be a cause of cancer. The latter belief, though entirely unfounded, is sometimes encountered today.

Vegetarian diets should probably be placed in this category—fads derived from fear of foods. Nutritionists do not challenge the statement that humans can subsist on a non-meat diet, but the foods must be selected with great care if a proper balance of nutrients is to be obtained.

A fourth type of food faddism emphasizes 'natural' foods, even carrying this to the extreme of insistence upon foods grown in soil enriched with 'natural' organic fertilizers.

Another fad involving confidence in the value of a food concerns white bread. Some people believe that white bread, as commonly purchased now, is nutritionally poor. This, of course, is to overlook the added milk, vitamins, and minerals—not to mention the proteins, other nutrients, and calories of the white bread itself.

To these four categories of food faddism, I would add one more—a catch-all for fads in which special devices, practices, and drugs are prominent. Here the motivations previously mentioned are frequently at work, as in the consumption of raw vegetables to cure cancer and the use of food pulverizers to prevent malnutrition. In a class by itself, however, is the indiscriminate use of pills for reduction of weight. The drugs commonly used are of three types. One is the nonspecific filler, such as methylcellulose, which gives a sensation of fullness. Another is the appetite depressant, usually amphetamine. And the third type is the metabolic stimulator, notably thyroid gland preparations, which act by accelerating caloric expenditure. Among reasons for using the term 'faddism' with regard to these agents is that they tend to divert attention from the main problem—overeating—and are often injurious in other ways.

W. H. Sebrell, Jr., M.D.
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The Young Diabetic

Panel Discussion

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Moderator

George M. Guest, M. D.†
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William B. Kennedy, M.D.§
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MODERATOR WHITE: The most important age periods in the management of the juvenile diabetic patient are infancy and adolescence. Some physicians dread the management of diabetes when the patient is under five years of age. The condition sometimes seems difficult to handle and it places extreme strain on the morale of the patients. Dr. Guest, what is your advice in regard to the diabetic infant?

DR. GUEST: In my opinion diabetic infants are not necessarily more difficult to manage than older children. I should say that the age of adolescence is a much more difficult period than that of infancy, but then of course, other problems are involved. As most of you know, I recommend the so-called "free-diet-glycosuric" regime which is a subject of continuing debate. (See editorials in DIABETES: *1*:487-89, Nov.-Dec. 1952.) In our clinic we have eighteen diabetic infants with onset of diabetes under the age of two years. Of these, eight were under one year of age when symptoms were first recognized. The youngest started glycosuria at nine days of age. The diagnosis was made by the astute mother because she had another diabetic child then aged one and one-half years. When she noted the new infant was passing a lot of urine, she tested it and found sugar. On admission to the hospital, the baby's blood sugar was 350 mg. per 100 cc. The urinalysis showed 3-plus glycosuria but no ketonuria. During twenty-four hours we determined the blood sugar every two hours and found it fluctuating between 300 and 500. Because there was no ketonuria, we felt that a period of observation before starting insulin would do no harm. After that brief period of observation the baby was given an initial dose of three units of protamine zinc insulin. During the next twenty-four hours the blood sugar fell progressively (determined at two-hour intervals) to 150 and then 100. Again, three units of protamine zinc insulin kept the blood sugar within normal range. (Let me stress the necessity for microchemical methods for following blood chemical changes in infants, whether diabetic or nondiabetic.) The baby was sent home on the fifth day, receiving two units of protamine zinc insulin daily. He was breast fed for ten months, on a demand schedule, with the dosage of protamine zinc varying from one to three units daily and solid foods offered at usual ages. (Please note that breast feeding is the ultimate in "free diet," while it lasts!) That child is now seven years of age and has not suffered any illness that required hospitalization. His urine is rarely free of sugar, but excessive glycosuria with polyuria is likewise rare. Transient ketonuria has occurred occasionally during intercurrent infections, but has always cleared up promptly with the administration of extra doses of quick-acting insulin. The insulin requirement increased slowly with age and increasing body weight, from five units a day at one year of age, to thirty-five units (globin insulin) a day at the present time.

Other practical suggestions may be pertinent here as a guide to facilitate the mother's daily routine of urine tests. Don't forget that if taken quickly a few drops of urine easily sufficient for testing for both sugar and acetone can be squeezed from a wet diaper. Another method we have used is to place a wad of absorbent cotton in a paper or soft plastic cup inside the diaper. The cotton retains a generous amount of urine that can be squeezed out easily. Also, there is a transparent soft plastic triangular diaper now on the market with a

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long tip to catch the urine. To obtain the urine sample the tip is simply cut off with a scissors to allow urine to run into a beaker. It is important to recommend to mothers all possible simple practical aids to facilitate home management of the diabetic infant.

I should like to stress the importance of alertness to avoid the crisis of ketonemic acidosis, insisting on the dictum that severe acidosis and coma should *never* occur if extra doses of insulin are given promptly when needed. Parents who fear insulin reaction are apt to decrease or omit insulin if an infant refuses food or vomits. They must be warned that the insulin requirement increases sharply during infections. Regardless of food intake they should be prepared and alert to give extra doses of insulin promptly if glycosuria increases and is accompanied by acetonuria.

MODERATOR WHITE: Thank you, Dr. Guest. Would you care to discuss the problems of the adolescent, Dr. Kennedy?

DR. KENNEDY: If we could solve the problems of the normal adolescent, we might begin to solve the problems of the diabetic adolescent.

The diabetic child is likely to have been fairly cooperative until he reaches adolescence when he begins to want to behave just like his fellow boys and girls. I think that many of the problems of this situation are best solved by trying to reason with these youngsters and helping them to adjust to a regime that will allow them to be as nearly like their friends as it is possible to be. Perhaps we have to modify our ideal program in handling the adolescent. Perhaps this is a period of life when diet freedom can with good reason be increased just a little, hoping that the need for this is temporary and will not establish a rule that will be carried beyond the adolescent stage.

However, at the same time as the youngster needs a little more freedom, he also begins to cooperate in other ways. He becomes more intelligent and you can reason with him a little more. He can respond to the education about diabetes more effectively. He is beginning to become an adult. You can look forward to a period following adolescence when better control returns and when stabilization of the diabetes becomes easier. Therefore, we can have hopes for the future and this helps us get through what is a very trying period.

Let us not forget, if you as a physician have established a relationship with your young diabetic patient which is ideal—one of trust, one of confidence, one of mutual exchange of ideas and cooperation—you are going to find far less trouble with him or her during the adolescent period than you will have if you are strangers apart and not able to cooperate with each other.

MODERATOR WHITE: A very important question is: How do you make the diagnosis of diabetes in children? Dr. Harwood?

DR. HARWOOD: It is not greatly different from the diagnosis of diabetes in adults. Glycosuria in the child is perhaps less apt to mean diabetes, but the diagnosis in the end will depend, as it does in the adult, on the blood sugar. A pathological blood sugar level in childhood has the same significance as it does in adulthood.

MODERATOR WHITE: We are dodging the issue, what is the diagnostic level for the blood sugar?

DR. HARWOOD: In general, I should say that a fasting blood sugar of 120 or higher, by the Folin-Wu method, is pathologic. A postprandial blood sugar of 200 mg. is also to be considered abnormal.

DR. GUEST: The fasting blood sugar level often may not offer critical help in the diagnosis of juvenile diabetes. A postprandial blood sugar is usually just as informative as a complete glucose tolerance test and nearly always will disclose frank diabetes. During a period of insidious onset of diabetes in children, with mild manifestations, the morning blood sugar level after overnight fasting may be even lower than normal; but it will be high after generous meals.

DR. HARWOOD: I didn't mean to imply that if the blood sugar was under 120 that that excluded the diagnosis of diabetes. In mild diabetes it is extremely common for the fasting blood sugar to be normal; yet the blood sugar after a meal, or a glucose tolerance test, may disclose the presence of diabetes. I think a test taken between an hour and an hour and a half after a hearty carbohydrate meal is to all intents and purposes a sugar tolerance test, and I prefer to get a blood test at that time rather than fasting.

QUESTIONER: How can you be sure about diabetes by a one-hour test? Suppose you have liver disease, or rapid emptying of the stomach, and why not a two-hour test?

DR. HARWOOD: Of course, one has to consider the patient's general condition in interpreting a single blood sugar test. If a patient has a condition known to affect carbohydrate metabolism, such as cirrhosis, thyrotoxicosis, and acute illness, one must be more cautious in diagnosing diabetes from a single abnormal blood sugar.

ROBERT L. JACKSON, M.D., (*Columbia, Missouri*): I should like to ask about the comments of Dr. White with regard to the accelerated needs of insulin in terms of one to three years after the initial regulation of the patient. It has been our experience (my associates and I

are analyzing data at the moment) that the linear growth is very intimately associated with its acceleration which we are seeing primarily after six weeks, three months, or certainly within the first six months after the initial regulation. As soon as the metabolic stores have been recovered and the patient transitorily has a chance to catch up, he will then start growing in height and concurrent with that his insulin requirement will follow a definite pattern highly correlated with his growth from there on. We have not observed the delay that was mentioned.

MODERATOR WHITE: I think I made the time element a little too specific. It was really approximate and I agree absolutely with Dr. Jackson's remark.

QUESTIONER: I should like to ask two questions: The first one, your definition of potential diabetes as evidenced by blood sugar findings in the glucose tolerance test. The second, the normal values fasting one-half hour, one hour and two hours after the ingestion of 100 gm. of carbohydrate?

MODERATOR WHITE: I think that was addressed to you, Dr. Harwood.

DR. HARWOOD: I try to avoid making a diagnosis of "potential diabetes" from a glucose tolerance test. As to the normal figures for a glucose tolerance test they are: fasting, 80 to 110 (using venous blood by the Folin-Wu method), in one-half hour 140 to 160, falling to normal in two hours, and in three hours the figure is often lower than the fasting level.

DR. KENNEDY: Dr. White, may I insert a practical note here.

MODERATOR WHITE: Please do.

DR. KENNEDY: In my experience the development of diabetes in the juvenile person is usually rapid. If we are seriously in doubt after applying all these scientific tests and can't say definitely the child is either perfectly normal or definitely diabetic, don't you think it might be safe to observe him closely and wait a few weeks? I realize that it is an advantage to find diabetes as early as we can. However, I don't think it is right to take a chance and treat a possibly normal child as though he were a diabetic on the suspicion that he just might possibly develop diabetes.

MODERATOR WHITE: Is there a definite correlation between added insulin requirement and dosage of cortisone, hydrocortisone or corticotropin? Will you answer that question, Dr. Guest?

DR. GUEST: This question regarding corticotropin directs attention to the role of various factors of stress in the diabetic; this certainly merits discussion. Adrenal cortical stimulation may be an important trigger mechanism that influences the onset of diabetes. Perhaps this mechanism is involved when a child suddenly develops frank symptoms of diabetes after infection (for example, streptococcal sore throat). In our hospital we recently observed the development of diabetes in a girl aged two and a half years who had suffered from severe asthma since the age of fourteen months, and who was treated with several courses of cortisone (each giving some relief of asthma) at various times from the age of eighteen months onward. After an unusually severe attack of asthma and another course of cortisone, she suddenly developed polyuria and glycosuria with persistent hyperglycemia. There was a family history of diabetes in a paternal aunt with onset at seventy years of age. We concluded that in this child, potentially diabetic from birth, the stress of asthma plus the administration of cortisone might have acted to precipitate manifestations of frank diabetes. Several investigators have reported that the administration of corticotropin or cortisone in nondiabetic persons leads to elevation of blood sugar, and in the diabetic patient to increased "insulin resistance." This effect disappears when the administration of corticotropin or cortisone is stopped. It is the "potentially" diabetic person (with genetic factors usually disclosed by a family history) that factors of stress may constitute a trigger mechanism.

MODERATOR WHITE: Here is a question we can all answer quickly and briefly. What growth standards do you use?

DR. GUEST: We have used Wetzel's grid, also the standards of Dr. Jackson and Dr. Harold Stewart.

MODERATOR WHITE: Dr. Kennedy, have you found choline to have a favorable effect in regard to insulin requirement?

DR. KENNEDY: I don't think choline has any place in our therapeutic armentarium at the present time.

MODERATOR WHITE: This is a very important question—what does the electroencephalogram show in the young diabetic who has many episodes of hypoglycemia?

We find that there is often an abnormal pattern; under stress slow waves may appear. Such patients may be subject to many questionable insulin reactions. When treated with phenobarbital or Dilantin or other anticonvulsant the episodes may disappear and it may seem easier to control the diabetes. In our experience this therapy usually has to be continued for about a year, perhaps two; then it can often be discontinued.

QUESTIONER: Dr. Kennedy, you have emphasized the advantage of multiple injections. Why are two doses of long-acting insulin necessary in the younger group of diabetics? Is its action more quickly dispelled or is it

destroyed by anti-insulin factors or some other factor?

DR. KENNEDY: If we give two doses of x units each of a long-acting insulin at twelve-hour intervals, the resultant rate of insulin absorption is much steadier than that obtained from one dose of 2x units each twenty-four hours. With the two-dose schedule, the absorption peak of one injection may coincide with a period of low absorption from the second injection, thus providing insulin to the body at a relatively constant rate. This effect is desirable in certain cases.

MODERATOR WHITE: Dr. Harwood, will you answer a question on diabetic coma? In the case of a girl aged thirteen years, the daily insulin requirement rose from twenty-four to eighty units after coma. Is it customary for the insulin requirement to rise very much after coma? Does the requirement remain high if it does go up?

DR. HARWOOD: It is my impression that there tends to be a slight increase in the insulin requirement following coma, but it is not always so. More regularly, however, there is a period of remarkable instability after severe acidosis. We have all seen the insulin requirement rise markedly and unaccountably after several years of diabetes, with or without coma.

QUESTIONER: Dr. White, did any of your patients who needed less insulin postpartum not have estrogen therapy?

MODERATOR WHITE: Yes, 5 per cent of the patients had no estrogen therapy.

In an unselected sample of our obstetrical diabetic population, if we divide the patients who received female sex endocrine therapy into two groups, with onset of diabetes under the age of fifteen, and with onset above fifteen years, 60 per cent of those whose diabetes started in childhood took less insulin after termination of pregnancy than their usual adult dose of insulin. Fifty per cent of these had more than a 50 per cent drop and 17 per cent of these had more than a 75 per cent drop. In contrast to this, those patients with onset of diabetes above the age of fifteen years had a 50 per cent drop in only 5 per cent of the group.

QUESTIONER: Is there a fixed scale of insulin dosage according to the amount of sugar shown by urine tests—5, 10, 15 or 20 units of insulin when the tests are 1-plus, 2-plus, 3-plus, or 4-plus? Sometimes insulin ordered after operations according to this scale has led to reactions—when 20 units of regular insulin have been given for 4-plus urine.

MODERATOR WHITE: Of course all insulin prescriptions have to be individualized for the patient, taking into account the requirement of the patient in the pre-surgical period, the age of the patient, and the impression of the severity or type of diabetes. There is no such fixed prescription which we use for our patients. The precipitation of hypoglycemia following surgery has been emphasized. After a glucose infusion, the first urinalysis may show sugar; this should be discarded and a second specimen should be used to guide the adjustment of the insulin dosage.

Dr. Harwood, I think you have more questions on diabetic coma.

DR. HARWOOD: How would you manage the patient in diabetic coma of long duration when the blood sugar is approximately 220 to 250 mg., particularly in respect to insulin dosage and earlier administration of glucose? I would use smaller doses of insulin and watch the blood sugar to see whether the smaller dosage was effective in lowering the blood sugar and relieving the ketosis. I suggest a dose of twenty to thirty units for a child, and forty to fifty units for an adult.

Again, in a patient with a blood sugar that low and with severe ketosis, I think it quite reasonable to start the administration of glucose earlier than one in a case in which the blood sugar is very high.

ROBERT L. JACKSON: I should like to make one comment. I think it is most important in children to base the insulin dosage on body weight rather than on a specific figure. I think one may really get in trouble in considering doses of ten, twenty, or forty units without regard to the body weight of the patient which of course varies tremendously from infant to full adult size.

MODERATOR WHITE: Dr. Guest, have you any comment?

DR. GUEST: On this question of insulin dosage, I feel strongly that it is not desirable or possible to arrive at a fixed dosage for long periods of time. The patient who is self-dependent and well trained can adjust the dosage of insulin daily, according to need. I might cite a case in point (Pediatrics, 1953, page 756). A boy, aged fourteen years, admitted to hospital in coma at the onset of the disease, remained in the hospital for seven days, then went home with his indoctrination seemingly complete, to live on a farm. He went home taking 100 units, a mixture of protamine zinc and regular insulin. During the next month he decreased the dosage, being guided by daily urine tests, until he got down to five units a day. He required only five or ten units of insulin a day between February and the end of March when he suddenly got a sore throat. According to the mother, when the family physician came to call and found the boy had lots of sugar and acetone in the urine he said, "Well, I'll treat his sore throat with

antibiotics, but I don't know anything about diabetes." The boy promptly said, "I do!"

The chart made from the record he kept through this whole period showed that during two days he increased his insulin dosage again up to 100 units. With his sore throat recovered he went back to school still taking 100 units. Again his glycosuria diminished rather rapidly and during the next month he decreased his insulin to ten units. He went through both periods of decreasing insulin requirement without ever having had an insulin reaction.

QUESTIONER: Does the blood lipid or cholesterol content parallel the degree of vascular sclerosis in infants?

DR. KENNEDY: Vascular sclerosis in infants isn't common enough to make us worry about this.

QUESTIONER: Please discuss the role of dietary fat in the prevention of vascular lesions in juvenile diabetes.

MODERATOR WHITE: There has been some excellent work by Kinsell and his associates who have shown that fat of vegetable origin appears to be less harmful than fat of animal origin. More and more we are thinking in terms of oleomargarine, peanut butter, olive oil and so forth.

QUESTIONER: In regard to the decreased insulin requirement of women in the puerperium, how long does it last? Do they continue their improvement? Are multiple pregnancies favorable, and shall we recommend frequent pregnancies and childbearing?

MODERATOR WHITE: Well, literally, we are doing that. The second and third pregnancies appear to be more favorable in lowering the insulin requirement than the first. The longest duration of lowered insulin requirement that we have observed has been ten years and the patients who showed this improvement have not gone back to their former high dose level. Dr. Jackson asked me if we could explain it on extra activity of the patient taking care of children and extra care in the diet because of added responsibility. We have weighed all of these things and do not think that that is the explanation for the altered requirement.

QUESTIONER: Do you recommend the use of salt by mouth in the early stages of acidosis before fluids are needed intravenously?

DR. HARWOOD: That is a good question. Sodium and potassium salts, carbohydrate and water all have an effect of protecting the patient to a certain degree from acidosis. If a patient is still able to eat or to drink, there is often no need for intravenous fluids. Frequent small feedings, with insulin ordered according to test, may be all the treatment needed in early acidosis.

MODERATOR WHITE: Hypoglycemia is a very serious problem in the young diabetic, and a question has been submitted regarding permanent damage. Dr. Guest, will you answer that?

DR. GUEST: It is something we all worry about. There are several cases recorded of children, apparently mentally normal, who showed evidence of cerebral damage and feeble-mindedness following a very severe prolonged hypoglycemic reaction.

MODERATOR WHITE: Dr. Harwood, I think you have a few more questions on diabetic coma.

DR. HARWOOD: Is there an explanation for the extreme restlessness one sometimes enccunters in a coma or acidotic patient? I can think of several explanations. Nausea, vomiting, and abdominal pain can make the patient restless. So can peripheral vascular collapse. The discomfort of air hunger may also contribute to his restlessness. I have observed restlessness in patients developing the syndrome of potassium deficiency, and I suppose it may be due in part to weakness of respiratory muscles.

MODERATOR WHITE: A question has been asked regarding the earliest age at which aneurysms in the ocular fundi have been observed. Dr. Guest says he hasn't seen any in children. I must admit that I have but they are extremely exceptional in childhood years. I have seen one at the age of fourteen. This child developed diabetes in 1922 and her past history had been characterized by many bouts of ketoacidosis.

QUESTIONER: We have been told the evils of giving too little insulin over long periods. Is it desirable to give as much insulin as possible without producing hypoglycemic reactions? And, should the insulin dosage be pushed up to tolerance?

DR. KENNEDY: I remember the statement of Dr. Francis Lukens, "The dose of insulin is *enough*." Of course we should give as much insulin as necessary to allow complete utilization of an adequate diet without producing hypoglycemic reactions. In other words, insulin dosage should be pushed up to tolerance assuming that dietary intake is proper in amount and hypoglycemic reactions are minimal in number and severity.

QUESTIONER: What is the role of fructose in the treatment of diabetic acidosis?

DR. HARWOOD: I have had no experience with the use of fructose. I have read that a goodly percentage of it, something like 60 to 70 per cent, becomes converted to glucose in the course of its metabolism and, therefore, I should feel that it is perhaps not a good thing to use in the early hours of treatment of diabetic acidosis. On the other hand, fructose does not require

insulin to be converted to glycogen and in the patient whose acidosis is coming under control it might be quite useful. Have you had any experience regarding this, Dr. Guest?

DR. GUEST: I might elaborate that a little bit. Dr. Best touched on this subject and has said that there is evidence that fructose can be utilized without insulin especially by muscles. There is an additional point with regard to the use of fructose in the acidotic patient. There is some experimental evidence that the utilization of fructose is less inhibited by acidosis (that is, by a low *p*H) than is the utilization of glucose.

MODERATOR WHITE: I have a group of questions: What is the effect of oxytoxics on blood sugar and insulin requirement? We have occasionally used pitressin for severe insulin reactions and the insulin requirement might be increased but I have had no experience.

Have any electroencephalogram changes been observed in cases of labile diabetes? These have been reported but not confirmed.

Dr. Richard Harvey reported the appearance of retinal microaneurysms, after cortisone administration to experimental animals. Are we advised to use cortisone for these lesions despite these findings? I am not quite sure what that question means. Ophthalmologists often use cortisone in solution in the eye and certainly no harmful effects have been produced. When corticotropin first came out, it seemed to me that perhaps corticotropin and cortisone might help in the problem of retinitis proliferans. Some twelve patients were treated with rather large doses of corticotropin, some of it intravenously, for a period of six weeks. Well, we precipitated massive hemorrhages which fortunately later resolved so I, for one, would not recommend it for the management of retinopathy.

Is there any information as to prediabetic determinations especially in the children of diabetic women? We think that the children of diabetic mothers have no greater susceptibility to diabetes than do the children of young diabetic fathers. To answer this problem to our own satisfaction we recalled 204 children of young diabetic parents, all of whom were under the age of twenty. Where both of the parents were identified as diabetic, 33 per cent had clinical diabetes and a total of 62 per cent had either clinical diabetes or an abnormal glucose tolerance curve. Where the mother was a diabetic, 9 per cent had clinical diabetes and 14 per cent had positive glucose tolerance curves. There were 100 of those. Eighty-five children of diabetic fathers were recalled and 9 per cent had clinical diabetes and 12 per cent had positive glucose tolerance curves. Whether the parent was a diabetic father or a diabetic mother, the susceptibility to diabetes appeared to be the same. We were alarmed at this high figure and wondered whether we should carry out eugenic advice further. There is some new work, however, that makes us a little bit less pessimistic about this. Biochemists have become interested in genetic and endocrine diseases and they are finding that carriers have some of the characteristics of the disease. We wonder if our positive tolerance curves may not be the identification of a carrier rather than of a prediabetic; at least we hope so.

QUESTIONER: I'd like to ask Dr. White one other question pertaining to this. Were the children of diabetic parents who showed signs of diabetes mainly in the older age groups?

MODERATOR WHITE: Yes, the cases of clinical diabetes, although one developed it at six.

QUESTIONER: Over twenty years, the incidence may be much higher?

MODERATOR WHITE: Yes, but there was an extraordinarily high incidence for children under the age of twenty. We expect only one child in about 2,500 of the average population to contract diabetes under the age of fifteen. Dr. Guest, do you wish to discuss family history?

DR. GUEST: I should like to sound a warning against accepting a negative family history from the hospital records. Follow up the cases in future years. The longer you follow the family history of a diabetic, the greater the chances are that you will find more cases among the relatives.

MODERATOR WHITE: A question on that important subject of vitamin B_{12}. Do you believe that B_{12} orally or parenterally is of value in the treatment of diabetic retinopathy? I certainly don't think it does any harm, but we have not been able to demonstrate any change in the frequency or the character of the retinopathy. I should like to ask other members of the group who see retinopathy what their experience is.

DR. HARWOOD: Well, I certainly agree with that.

MODERATOR WHITE: How much regular insulin may be mixed with NPH or lente to retain the individual effect of each insulin?

DR. GUEST: I should say that's settled by trial and error.

MODERATOR WHITE: I agree to that. The advantage of lente and NPH insulin over protamine insulin in this respect is that they do not adsorb large quantities of rapidly acting insulin, so that one does not reverse ratios as one does in using mixtures of rapidly acting insulin with protamine insulin.

ABSTRACTS

Abrams, Gerald D.; Baker, Burton L.; Ingle, Dwight J.; and Li, Choh Hao (*Dept. of Anat., Univ. of Michigan Med. Sch., Ann Arbor, Mich., Res. Labs., Upjohn Co., Kalamazoo, Mich., and Dept. of Biochem., Univ. of Calif., Berkeley, Calif.*): THE INFLUENCE OF SOMATOTROPIN AND CORTICOTROPIN ON THE ISLETS OF LANGERHANS OF THE RAT. Endocrinology *53*:252-60, September 1953.

The effect of somatotropin on beta cells was variable and probably insignificant but corticotropin produced islet enlargement and hypertrophy and degranulation of the beta cells. Somatotropin and corticotropin administered simultaneously produced qualitatively the same effect as that of corticotropin alone.

Alpha cell size was increased by either hormone alone or both together but the difference between the means of treated and control groups was significant only with somatotropin.

Bass, Wm. P.; Watts, D. T.; and Chase, Harold F. (*Depts. of Anesthesiology and Pharmacol., Univ. of Virginia, Charlottesville, Va.*): ETHER HYPERGLYCEMIA AS INFLUENCED BY PREMEDICATION AND PENTOTHAL INDUCTION. Anesthesiology *14*:18-22, January 1953.

This series of studies has shown that the usual clinical doses of morphine alone and of barbiturates plus morphine used as anesthetic premedication have in themselves no significant effect on blood dextrose levels in man. The addition of barbiturate premedication before nitrous oxide-ether anesthesia does not significantly inhibit the blood dextrose rise when compared with premedication with morphine only. Pentothal induction of ether anesthesia produces a statistically significant inhibition of ether hyperglycemia.

Bollman, Jesse L.; Flock, Eunice V.; Grindlay, John H.; Mann, Frank C.; and Block, Melvin A. (*Sects. of Biochem., Surg. Res. and Div. of Experimental Med., Mayo Foundation, Rochester, Minn.*): ACTION OF GLUCOSE AND INSULIN ON FREE AMINO ACIDS OF THE DEHEPATIZED DOG. Am. J. Physiol. *174*:467-70, September 1953.

In the absence of the pancreas, administration of glucose does not alter the accumulation of free amino acids that occurs after total removal of the liver. The administration of insulin depresses this accumulation of amino acids. These observations suggest that the nitrogen-sparing action of glucose when the pancreas is present is caused by stimulation of the secretion of insulin. Insulin diminishes the amount of free amino acids in muscle as well as in plasma apparently by increasing the rate of incorporation of free amino acids into protein. In contrast to its great effect in muscle, insulin does not alter the concentration of total free amino acids or of glutamine in the brain.

Brun, C.; Gormsen, H.; and Hilden, T.: DIABETIC NEPHROPATHY REVEALED BY RENAL BIOPSY AND RENAL FUNCTION TESTS. Ugesk. laeger *115*:513, Apr. 2, 1953 (Abstr. in J.A.M.A. *152*:1575, Aug. 15, 1953).

Renal biopsy revealed diffuse glomerular changes in six out of twelve cases of diabetes mellitus, diffuse nodular changes in four, and completely hyalinized glomeruli with remnants of noduli in one. In four cases without definite clinical signs of diabetic renal affection, glomerular changes were demonstrated. The biopsies apparently support the theory that diabetic nephropathy starts as a diffuse hyalinization in the basal membranes of the glomerulus loops and that the nodular changes are a further development of the diffuse changes. Glomeruli with marked changes due to diabetes in some cases have an essentially greater filtration ability than could be assumed from the histological picture.

Chaikoff, I. L.: METABOLIC BLOCKS IN DIABETES. Nutrition Rev. *11*:312-14, October 1953.

Liver slices from diabetic rats incubated with C^{14} labeled glucose showed markedly reduced carbon dioxide formation and almost total abolition of fatty acid synthesis. When C^{14} labeled fructose was used the carbon-dioxide formation was the same from normal and diabetic livers but the fatty acid synthesis was markedly reduced. The author suggests that absence of insulin reduces the phosphorylation of glucose to glucose-6-phosphate since it was shown that phosphohexoseisomerase activities of normal and diabetic liver were identical.

High fructose feeding before killing restores the ability of diabetic liver slices to convert acetate to fatty acids, and this apparent block is a secondary effect of a block in glucose utilization rather than primary due to lack of insulin.

Cobley, J. F. C. C.; and Lancaster, H. O. (*Royal Hosp. for Women, Paddington, New South Wales, and Sch. of Public Health and Trop. Med., Sydney, Australia*):

CARBOHYDRATE TOLERANCE IN PREGNANCY. M. J. Australia *1*:171-75, Feb. 5, 1955.

One hundred and fifty-eight pregnant women have been subjected to glucose tolerance tests at intervals throughout pregnancy. The results are presented with the following conclusions: Carbohydrate metabolism as measured by the glucose tolerance test in pregnant women undergoes little change during pregnancy. The fasting blood sugar level of pregnant women is within the normal range. The peak of the glucose tolerance curve in pregnancy occurs at the anticipated time in most cases, but can be expected to be delayed in some women. The fall of the curve to normal takes two hours in most cases, but is delayed beyond two hours in perhaps one-quarter of pregnant women.

Cooper, Robert R. (*Dept. of Ophthalmology, Univ. of Minnesota Med. Sch., Minneapolis, Minn.*): DIABETIC RETINOPATHY. Journal-Lancet *73*:399-402, October 1953.

A discussion of the incidence and relation to duration of diabetes, the ophthalmoscopic picture, and the differential diagnosis is given.

Crampton, Joseph H.; Palmer, Lester J.; and Reeves, Robert L. (*Seattle, Wash.*): THE OFFICE AND HOME MANAGEMENT OF DIABETES. M. Clin. North America 1097-1112, July 1953.

The authors advocate a yearly urinalysis for all patients entering a doctor's office using a specimen of urine obtained one to two hours after eating. If glycosuria is found, a post-prandial blood sugar test should be made. The indications for a glucose tolerance test are discussed with instructions for the preparation for the test and its technic.

In treatment, they believe that an accurately controlled diet is essential. The indications for insulin therapy and the types of insulin available for use are presented. Their criteria of adequate control are presented, with the necessary modifications in the elderly patient.

The control of diabetes during an acute illness is outlined. It is emphasized that the diabetic should always take his usual amount of long-acting insulin. Additional regular insulin taken three times a day may be needed. The amount is determined by the degree of glycosuria. The home treatment of mild diabetic acidosis is described.

The special problems of diabetes and pregnancy are discussed. Four general rules are presented with a brief outline of the medical management of the patient.

Creutzfeldt, Werner (*Medizinischen Universitatsklinik Freiburg i. Br.*): ON THE FUNCTION OF ALPHA-CELLS OF THE PANCREATIC ISLANDS. CHANGES IN THE ALPHA-CELLS IN CASES OF LIVER DAMAGE, STRESS AND HYPOGLYCEMIA. Klin. Wchnschr. *32*:819-20, Sept. 1, 1954.

The degranulation and vacuolation of the alpha-cells following various poisonings (cobaltous chloride, synthalin, carbon tetrachloride, phosphorus) often occur along with hypoglycemia, fatty infiltration of the liver, glycogen depletion and adrenalin burdening, but that a single factor is not sufficient for these occurrences. Further investigation shall show whether there is a uniform disturbance in the intermediary metabolism from which conclusions can be drawn as to the role of the alpha-cell hormone in the organism. The relationship of this hormone to the liver metabolism is apparently close and opens interesting vistas to the liver pathology. Whether lipocaic is identical with glucagon is questionable (German)

Derus, Gerald J.; Musser, Marc J.; and Lorenz, Thomas H. (*Madison, Wis.*): HYPERVENTILATION AND PSEUDO-HYPOGLYCEMIC REACTIONS IN DIABETES MELLITUS. J.A.M.A. *152*:1113-16, July 18, 1953.

Certain diabetic patients present symptoms simulating mild to moderate hypoglycemia as a result of hyperventilation. Successful management entails appropriate psychotherapy and correction of the faulty breathing pattern under stress, in addition to the usual medical measures.

Detailed study of fourteen diabetic patients who were having frequent "insulin reactions" revealed the following facts: 1. Reactions that were not accompanied by hypoglycemia occurred commonly in this group. 2. All the patients were excessively anxious and also were hyperreactive to two minutes of hyperventilation. 3. The symptoms induced by overbreathing reproduced in these patients their typical symptoms of "insulin reactions." 4. None of the patients had electroencephalographic evidence of cerebral dysrhythmia (even with hyperventilation).

It is concluded that, when the hyperventilation syndrome occurs in anxious diabetic patients, it can produce symptoms that stimulate, and thus are easily misinterpreted as true insulin reactions.

Donahue, Hugh C. (*Boston, Mass.*): UNUSUAL TYPE OF DEGENERATIVE RETINOPATHY. Am. J. Ophth. *36*: 921-24, July 1953.

A case of severe retinopathy is presented occurring in the absence of hypertension, arteriosclerosis, diabetes mellitus, or kidney disease. There were only two positive

findings, namely, obesity and a markedly elevated serum cholesterol.

Foreign Letters (*Italy*): NONINFECTIOUS LIVER DISEASES. J.A.M.A. *153*:233, Sept. 19, 1953.

Among the liver diseases associated with an altered carbohydrate metabolism, the author distinguished abnormalities of the liver in diabetes from the disorders due to glycogenesis (Gierke's disease).

Freeman, R. V.; Jones, T. E.; and Palmer, J. J. (*Veterans Administration Center and Dept. of Path., Univ. of California Sch. of Med., Los Angeles, Calif.*): THREE-YEAR FOLLOW-UP OF PATIENTS DEVELOPING EOSINOPHILIA DURING INSULIN COMA THERAPY. A.M.A. Arch. Neurol. & Psychiat. *71*:501-10, 1954.

It was shown that a definite eosinophilia developed in some patients during insulin coma therapy. It is suggested that further investigation of metabolic changes during insulin coma therapy is warranted in order to determine the value of the blood eosinophil (or some other test) as an aid in predicting the probability of prolonged remission of a schizophrenia.

Gibbs, F. A.; and Murray, E. L. (*Veterans Administration Hosp., Hines, Ill.*): HYPOGLYCEMIC CONVULSIONS: THREE CASE REPORTS. Electroencephalog. & Clin. Neurophysiol. *6*:674-78, November 1954.

Blood sugar studies and electroencephalographic recordings on two patients undergoing insulin shock treatment and one patient with spontaneous hyperinsulinism show that spike seizure discharges of high voltage, which are indistinguishable from those that are common in epilepsy, can be recorded from the scalp in association with hypoglycemic convulsions. The hypoglycemic cortex is capable of producing (or participating in), high voltage discharges; whether the primary site of such discharges is cortical or subcortical is not indicated, but the fact that focal high voltage spikes may occur suggests that in some cases the primary discharge is cortical.

Goodman, Joseph I. (*Cleveland Heights, Ohio*): THE SPECIFIC VASCULAR LESIONS OF DIABETES MELLITUS. II RETINOPATHY AND INTERCAPILLARY GLOMERULOSCLEROSIS. Am. J. Ophth. *36*:957-66, July 1953.

The possibility presents itself that the typical retinal and glomerulosclerotic lesions in diabetes mellitus are related somehow to disturbances in adrenal corticosteroid balance and their effect on the supporting fibrous tissue of the smaller vessels. This concept involves some aspects of the stress mechanism. If this hypothesis should be borne out, there may be some hope to counteract incipient retinal and renal damage by better treatment of the patients' diabetes thereby avoiding stress. Research should be concentrated along these lines. Eventually prophylaxis and newer therapeutic aids may prove to be helpful in checking the progress of these complications.

Gujral, M. L.; Chowdhury, N. K.; and Srivastava, R. S. (*Dept. of Pharmacol., Lucknow Univ., Lucknow, India*): INDIGENOUS DRUGS IN EXPERIMENTAL DIABETES. Indian M. Gaz. *89*:141-46, March 1954.

1. Normal blood sugar of rabbits kept on a standard diet was estimated. No effect on the level of blood sugar could be demonstrated after oral administration of Eugenea jambolana seed powder in these animals.

2. Chronic alloxan diabetes was produced by giving repeated small doses of alloxan intravenously and intraperitoneally.

3. The treatment of the animals by *Eugenea jambolana, F. glomerata, F. religiosa,* and *Melia azadirachta* proved ineffective.

Handelsman, Milton B. (*Coll. of Med., State Univ., New York, and Long Island Coll. Hosp., Brooklyn, N. Y.*): OBJECTIVES IN DIABETES. New York State J. Med. *53*:1427-30, Jan. 15, 1953.

The author discusses the following topics: preventing death in diabetes; giving adequate nutrition to the diabetic; planning therapy to conform with normal living; improving the psychologic, social, and economic status of patients; safeguarding the pregnancies of diabetic women; preventing and more effectively treating degenerative complications; and applying the newer knowledge concerning the endocrines in diabetes.

Heinsius, E.: CAN THE OPHTHALMOLOGIST TREAT DIABETIC RETINITIS? Wien. klin. Wchnschr. *65*:57-58, 1953 (Abstr. in Am. J. Ophth. *36*:1010, July 1953).

In addition to regulation of the diabetes, the author discusses the use of calcium, rutin, vitamin K, testosterone, and priscoline.

Hranilovich, George T.; and Baggenstoss, Archie H. (*Sect. of Path. Anat., Mayo Clin., Rochester, Minn.*): LESIONS OF THE PANCREAS IN MALIGNANT HYPERTENSION. REVIEW OF ONE HUNDRED CASES AT NECROPSY. A.M.A. Arch. Path. *55*:443-56, June 1953.

Routine histologic sections of the pancreas obtained at necropsy in 100 cases of malignant hypertension have been reviewed and correlated with analyses of clinical data in the cases.

Moderate to severe arteriolosclerosis occurred in sixty-eight cases. Infarcts of the pancreas were encountered in seven cases, focal parenchymal necrosis in twenty-

one cases, and foci of atrophy in seventy-three.

Vascular alterations were the most important factor in the production of parenchymal lesions such as infarction, focal parenchymal necrosis, atrophy, and fibrosis. Although arterial thrombosis could be demonstrated in six of the seven cases of pancreatic infarction, it could not be demonstrated in any of the twenty-one cases in which parenchymal necrosis was noted. It is suggested that congestive cardiac failure and shock in the presence of severe arteriolosclerosis may be important factors in the production of parenchymal necrosis.

Arteriolosclerosis of the pancreas is strongly indicative of, but not pathognomonic for, malignant hypertension. Vascular factors by themselves are not important etiologic factors in acute hemorrhagic pancreatitis.

Huggett, A. St. G.; Warren, F. L.; and Winterton, V. N.: FRUCTOSE METABOLISM IN THE FETUS OF THE SHEEP. Abstracts Communs. 1st Intern. Congr. Biochem., pp. 9-10, 1949 (Abstr. in Chem. Abstr. *45*:5795, July 10, 1951).

Intravenous injection of glucose into pregnant sheep causes hyperglycemia in the ewe; in the fetus, hyperglycemia is delayed and there is a hyperfructosemia reaching a maximum after four hours. When glucose is injected into the fetal circulation, the immediate hyperglycemia is followed by prolonged fetal hyperfructosemia. The source of the fructose is the placenta and not the fetus.

Ingle, Dwight J.; Beary, Dexter F.; and Purmalis, Andrejs (*Res. Labs., Upjohn Co., Kalamazoo, Mich.*): COMPARISON OF EFFECT OF PROGESTERONE AND 11-KETOPROGESTERONE UPON GLYCOSURIA OF PARTIALLY DEPANCREATIZED RAT. Proc. Soc. Exper. Biol. & Med. *82*:416-19, March 1953.

Partially depancreatized force-fed rats were injected with 1 to 100 mg. per day of progesterone and 1 to 32 mg. per day of 11-ketoprogesterone. Very large doses of progesterone (greater than 32 mg.) caused exacerbation of the diabetes and 11-ketoprogesterone was found to be significantly more potent (eight times) in this respect. The diabetogenicity of 11-ketoprogesterone is manifest in either the presence or absence of the adrenal glands.

Ingle, Dwight J.; Meeks, Robert C. (*Res. Labs., Upjohn Co., Kalamazoo, Mich.*): SUPPRESSION OF GLYCOSURIA DURING ADMINISTRATION OF LARGE DOSES OF ASPIRIN TO FORCE-FED PARTIALLY DEPANCREATECTOMIZED RATS. Am. J. Physiol. *171*:600-03, December 1952.

Upon subcutaneous administration to partially depancreatized male rats force-fed a medium carbohydrate diet, at a weekly dose level of 40, 80, and 160 mg. per day, aspirin produced a marked suppression of glycosuria, with the degree of suppression proportional to the size of the dose. Amelioration of the glucosuria was accompanied by reduction in hyperglycemia but not by decrease in urinary nonprotein nitrogen. The mechanism of this action by aspirin is unknown, and cannot be explained as a nonspecific effect of a toxic compound.

Jaques, William E. (*Dept. of Path., Peter Bent Brigham Hosp. and Harvard Med. Sch., Boston, Mass.*): THE INCIDENCE OF PORTAL CIRRHOSIS AND FATTY METAMORPHOSIS IN PATIENTS DYING WITH DIABETES MELLITUS. New England J. Med. *249*:442-45, Sept. 10, 1953.

The livers of patients dying with diabetes mellitus from 1928 to 1950 were examined for evidence of portal cirrhosis. A total of 177 patients comprised this study and were compared with a similar number of patients serving as controls.

The incidence of portal cirrhosis in the diabetic patients was 16.3 per cent, whereas only 8.4 per cent of the control series were found to have cirrhosis. It was believed that this represented a statistically valid difference. Fatty livers were observed in 57 per cent of the diabetic as compared with 36.1 per cent of the nondiabetic patients. Cirrhosis played a major part in 4.5 per cent of the deaths from diabetes, excluding the alcoholic patients, in this series.

Jensen, C. C.; and Bergqvist, Nils: GONADAL FUNCTION IN DIABETIC MALES. Acta Endocrinol. *15*: 351-54, April 1954 (Abstr. from Prensa méd. argent. *41*:2470, Aug. 20, 1954).

Urinary 17-ketosteroids were determined in 115 diabetic patients (sixty-three males and fifty-two females). A sex difference was noted in the age group between twenty and thirty-nine years, the male values for 17-ketosteroids being lower than normal. The female group did not show any significant deviation from normal values for this group. These differences are interpreted as hypogonadal state occurring in the male group. However, the occurrence of secondary gonadal insufficiency is possible, since gonadotropins were found low in some cases. (Spanish)

Jordan, William R. (*1631 Monument Ave., Richmond, Va.*): THE DIAGNOSIS OF DIABETES. Virginia M. Month. *82*:136-37, March 1955.

Typical symptoms of diabetes associated with much glycosuria are strong evidence of diabetes, but patients

can lose weight, feel weak, and admit urinary frequency and a dry mouth without having diabetes. Joslin's criterion of glycosuria related to food intake and abnormal elevation of the blood sugar remains the most reliable standard for the presence of the disease.

In a review of the records of 100 diabetic patients some interesting facts were noted. Of the 100 patients, only ten sought medical care for the classical triad of diabetic symptoms—hunger, thirst, and polyuria. Yet eighty more admitted having these symptoms or others often produced by diabetes, such as weight loss, languor, weakness, and nocturnal leg cramps. Either the patient earlier failed to consult his doctor about these symptoms or the doctor failed to make the proper urine test to reveal the presence of the disease. In four cases, diabetic coma was present before sugar was found.

In fourteen cases glycosuria was first found by routine examination for insurance, work, or school, or by routine health examination. Of these fourteen, however, eight had definite symptoms, and only five were persons without symptoms.

Many more cases, vulvovaginitis, balanitis, foot infections and other local infections led the patient to seek treatment; and twelve cases were found when they were seen for conditions unrelated to diabetes. An occasional case is found because of blurred vision as a result of disturbed water balance.

Joslin, Elliott P. (*George F. Baker Clin., Boston, Mass.*): THE PATIENT WHO CONTROLS DIABETES. Postgrad. Med. *14*:268-69, September 1953.

Dr. Joslin briefly discusses the purpose of the Quarter Century Victory Medal, patients who have won it, the relationship of lack of complications to control, and the future of the Quarter Century Victory Medal.

Kallee, Ekkehard (*Medizinischen Universitatsklinik Tubingen*): INSULIN LABELED WITH RADIOACTIVE IODINE (I^{131}). II. RANGE OF APPLICATION AND LIMITS OF METHOD OF DETERMINATION. Klin. Wchnschr. *32*: 508-09, June 1, 1954.

Through autoradiographs of paper electrophoresis strips up to 10^{-9} gm. of insulin labeled with radioactive iodine (I^{131}) can be determined. Human, rat, and guinea pig sera differ in their ability to weaken the specific absorption of calf insulin on filter paper. According to our experiments to date, human serum is most suitable for the specific insulin determination because here—in contrast to rat and guinea pig sera—the band characteristic insulin—I^{131} appears only when nonradioactive carrier insulin is added. (German)

Keys, Ancel; and Brozek, Josef (*Lab. of Physiol. Hygiene, Sch. of Public Health, Univ. of Minnesota, Minneapolis, Minn.*): BODY FAT IN ADULT MAN. Physiol. Rev. *33*:245-325, July 1953.

The author exhaustively reviews methods of direct and indirect estimation of body fat, evaluation of body weight and fatness, methods of measurement of subcutaneous fat, determination of body fat by densitometric and body water technics, and variations in body fat content in relation to age, physical activity, body build, changes in weight, and basal metabolism.

Mackler, Bruce; and Guest, George M. (*Children's Hosp. Res. Found. and Dept. of Pediat., Univ. of Cincinnati, Cincinnati, Ohio*): EFFECTS OF ACIDOSIS ON UTILIZATION OF FRUCTOSE AND GLUCOSE IN THE ISOLATED RAT DIAPHRAGM. Am. J. Physiol. *174*:487-90, September 1953.

The rate of phosphorylation of glucose and fructose by hexokinase in isolated rat diaphragm was decreased when the *p*H of the medium was reduced from 7.50 to 7.00. Lowered *p*H did not affect the phosphorylation of fructose by fructokinase. Studies on the effects of *p*H on the activities of hexokinase and fructokinase in pure systems yielded results in accord with those of the experiments on rat diaphragm. It is probable that fructose metabolism in the intact animal proceeds almost entirely by way of the fructokinase system, the presence of this enzyme permitting such animals to utilize fructose at normal rates during states of acidosis.

Nardi, George L. (*Dept. of Surg., Harvard Med. Sch., Boston, Mass.*): PHOSPHOLIPID SYNTHESIS IN PATIENTS WITH PANCREATIC DISEASE. RADIOACTIVE PHOSPHORUS AS MEASURE. A.M.A. Arch. Surg. *69*:726-31, November 1954.

The rate of synthesis of radioactive phosphorus into plasma phospholipid was determined for five patients with pancreatic disease. This rate of synthesis was diminished as compared with that for two normal (control) patients.

Ney, Genevieve J. (*N. Y. Med. Coll., Flower and Fifth Ave. Hosps., New York, N. Y.*): THE JUVENILE DIABETIC. A SURVEY OF THE RECENT LITERATURE. Arch. Pediat. 70:175-84, June 1953.

A survey of recent literature pertaining to diabetes is made, and from it, the author comments on the present-day status of the juvenile diabetic.

Paul, Jerome T. (*Chicago, Ill.*): CALCIFIED CYST OF THE PANCREAS. Am. J. Digest. Dis. 20:136-37, May 1953.

The author briefly discusses the three most common cysts of the pancreas that become calcified. There are the echinococcus, dermoid, and pseudocyst.

A case report of a fifty-four-year-old white male diabetic with a history of trauma to the upper abdomen is presented. Palpation of the abdomen revealed a grapefruit-sized mass in the upper abdomen. Calcified cyst was demonstrated by X ray. A discussion follows.

Pogue, William G.; Hall, Harold E.; and Hawthorne, Edward W. (*Dept. of Physiol., Coll. of Med., Howard Univ., Washington, D.C.*): INSULIN SENSITIVITY STUDIES IN THE DOG FOLLOWING CHANGES IN PLASMA, WHOLE BLOOD, AND CORPUSCULAR GLUCOSE. Am. J. Physiol. *174*:235-37, August 1953.

Insulin sensitivity studies were performed following changes in plasma, whole blood, and corpuscular glucose concentration. Thirty minutes after the injection of insulin, the glucose concentration was decreased in all the blood phases. Expressed as average percentage decrease the changes were: plasma 52.3 per cent, whole blood 40.9 per cent, and corpuscles 21.1 per cent. Over the same time interval, the glucose distribution ratio increased from 0.637 to 1.129. These data suggest that changes in plasma glucose concentration offer the more accurate measure of the insulin sensitivity of the dog.

Queries and Minor Notes: OVERWEIGHT AND LONGEVITY. J.A.M.A. *152*:1084, July 11, 1953.

A mortality study of overweight persons by Dublin and Marks showed long range benefit from weight reduction. Among both men and women, the death rate after weight reduction was substantially less than that for all of the overweight persons studied. Among the men, the reduction was of the order of one fifth and among the women about one third. This is perhaps the best evidence produced to date that weight control pays and is also the most practical approach now available to the problem of preventing or retarding major degeneration diseases of middle and later life. The question particularly referred to diabetes and circulatory diseases.

Robel, G.: GLYCOSURIA AND HYPERGLYCEMIA FOLLOWING TREATMENT WITH P-AMINOSALICYLIC ACID. Tuberkulosearzt 7:224, April 1953 (Abstr. in J.A.M.A. *152*:1488, Aug. 8, 1953).

Robel observed elevation of the blood sugar curve in a number of patients who were treated with *p*-aminosalicylic acid. In most cases, the hyperglycemia was reversible, but prolonged administration of the *p*-aminosalicylic acid is capable of producing irreversible changes in the insular apparatus of the pancreas and that it is advisable that fasting blood sugar determinations be made in addition to the usual tests performed during prolonged treatment with this drug, such as differential blood cell counts, determination of hemoglobin value, and urinalysis.

Russell, Alfred; and Fearing, Samuel J. (*New York, N. Y., and Southbridge, Mass.*): CAVERNOUS SINUS THROMBOSIS IN A DIABETIC: REPORT OF A CASE. Oral Surg. *8*:372-77, April 1955.

A case report of cavernous sinus thrombosis and brain abscess in a diabetic patient is presented and discussed. Acute infections, including those of the oral cavity, may contribute in activating a latent diabetic factor. The pain concomitant with oral infection may so contribute to nutritional inadequacies as to reduce the patient's resistance to infection. The oral surgeon must maintain a state of constant care and caution when treating fulminating dental infection, particularly when associated with systemic conditions.

Saslow, Benjamin (*Presbyterian Hosp., Newark, N. J.*): PRESENT STATUS OF THERAPY WITH LIVER EXTRACT FOR INJECTION. Postgrad. Med. *16*:178-85, September 1954.

A brief report is given of personal experience in treating eighteen patients with diabetic neuropathies employing a crude extract of pregnant beef liver. Of the eighteen patients treated, six showed considerable or striking improvement and four others showed some improvement which could have been ascribed to this special liver extract.

Seldin, Donald W. (*Dept. of Internal Med., Southwestern Med. Sch., Univ. of Texas, Dallas, Tex.*): GLUCOSE IN THE DEVELOPMENT AND TREATMENT OF DIABETIC ACIDOSIS. Texas J. Med. *49*:738-43, October 1953.

Studies were made of the effect of glucose administered in large quantities to normal human subjects. They are found to be of value in understanding the distortions of electrolyte metabolism characteristic of diabetic acidosis. To counteract these disturbances of diabetic acidosis, insulin, normal saline or Ringer's lactate solution, glucose, and potassium play important roles.

Sheppe, W. M. (*Dept. of Internal Med., Wheeling Clin., Wheeling, W. Va.*): NEUROPATHIC (CHARCOT) JOINTS OCCURRING IN DIABETES MELLITUS. Ann. Int. Med. *39*:625-29, September 1953.

The case reported illustrates the development of lysis

and absorption of the metatarsal and phalangeal bones in the right foot of an obese female diabetic. These changes are believed to be secondary to a proved diabetic neuropathy and are comparable to those occurring in other diseases producing neuropathic joint lesions. The authors were especially impressed by the absence of infection, the freedom from pain, the presence of findings indicative of diabetic neuropathy and retinopathy, and the integrity of the circulation of the involved foot.

Sherrill, James W. (*Scripps Metabolic Clin., La Jolla, San Diego, Calif.*): DIABETES IN CHILDREN: SOME PRACTICAL AND THEORETICAL CONSIDERATIONS IN MANAGEMENT. Texas J. Med. *49*:743-48, October 1953.

There is sufficient pre-existing information concerning the factors which regulate diabetes to encourage one to maintain good control of the disease; some of these are the control of obesity, a regulated diet of adequate calories sufficient for nutrition and growth but avoidance of a high caloric diet, and chemical control of hyperglycemia and glycosuria. There is no scientific evidence that hyperglycemia is harmless but considerable evidence to show that it is harmful. Adequate control is not determined by the child's appearance or his sense of well-being for these may be misleading. One common error in the management of diabetes is the use of too little insulin or the attempt to control severe or long-duration diabetes with one dose of any type of insulin. The author believes that Kimmelsteil-Wilson disease is confined to the group of patients who follow a so-called free diet. The report is based on thirty-five years experience with four hundred children who developed diabetes at fifteen years or younger.

Shonds, Harley C.; and Menzer, Doris (*Boston State Hosp., Boston, Mass.*): EOSINOPHIL VARIATION IN THE COURSE OF INSULIN COMA THERAPY. Am. J. Psychiat. *109*:757-66, April 1953.

The authors present a paper on the reaction of a group of schizophrenic patients to insulin shock. The response as determined by eosinophilic count is discussed both early and late in the course of insulin coma therapy.

Siedhoff, W.: FREQUENCY OF CONCURRENCE OF DIABETES AND TUBERCULOSIS. Tuberkulosearzt 7: 225, April 1953 (Abstr. in J.A.M.A. *152*:1489, Aug. 8, 1953).

In the course of roentgenologic examination of 2,962 patients with diabetes mellitus, Siedhoff discovered that 7.6 per cent had pulmonary tuberculosis. Reports in the literature indicate that the incidence of tuberculosis in diabetic patients varies from 2 to 8.4 per cent. The two diseases concur more frequently in men than in women. The 2,962 diabetic patients observed by the author included 1,158 men, of whom 12.2 per cent had tuberculosis; the ratio of men and women was 2.5:1. In the literature, it has been estimated that tuberculosis is from five to ten times as frequent in diabetics as in the general population. The author found that in 1950, in West Berlin, tuberculosis was four times more frequent in diabetic patients than in the general population. This patient material was unusual, since the incidence of tuberculosis had increased during World War II and the blockade in 1949. Following the lifting of the blockade in 1949, new cases and recurrences of diabetes increased considerably, particularly among women.

Sifontes, José E.; Williams, R. D. Brooke; Lincoln, Edith M.; and Clemons, Helen (*Dept. Pediat., New York Univ. Coll. Med., and Chest Clin. of Children's Med. Serv., Bellevue Hosp., New York, N. Y.*): OBSERVATIONS ON THE EFFECT OF INDUCED HYPERGLYCEMIA ON THE GLUCOSE CONTENT OF THE CEREBROSPINAL FLUID IN PATIENTS WITH TUBERCULOUS MENINGITIS. Am. Rev. Tuberc. *67*:732-54, June 1953.

The results of two-hour curves showing the passage of glucose from the blood into the cerebrospinal fluid following intravenous injection of glucose are reported. Five children without meningitis and six children with healed tuberculous meningitis showed similar curves, characterized by an increase in the glucose concentration of the lumbar and cisternal fluid of 30 to 60 mg. per 100 ml. above initial values; the maximum increase occurred between 45 and 120 minutes. The cisternal values were always slightly higher than the lumbar values. Abnormal curves were obtained in children with active tuberculous meningitis and in children with hydrocephalus resulting from tuberculous meningitis. The lumbar and cisternal curves in these patients were conditioned by the presence of block or by the administration of the streptomycin through the lumbar subarachnoid space. With improvement in the tuberculous meningitis, the abnormalities of the glucose curves disappeared.

Sindram, I. S. (*Netherlands*): PREGNANCY AND DIABETES. Nederl. tijdschr. geneesk. *97*:605-10, March 7, 1953.

In Holland at present 2,000 diabetic women became pregnant as contrasted with 150 diabetic pregnant women of thirty years ago. Diabetes during pregnancy had a tendency to ketosis and the carbohydrate tolerance decreases especially in the last months of pregnancy. The greater incidence of abortions in diabetic women is thought to be due to the hypertrophy of the islet of Langerhans occurring in the pancreas of the fetus. (Dutch)

Society Proceedings: DIABETES AND PHOTOGRAPHY. Am. J. Ophth. 36:986-87, July 1953.

Ernest Rosenthal of Hartford, Connecticut, presented photographs of the ocular fundi in cases of diabetes.

Stearns, Samuel (*Med. Serv. and Abraham Rudy Diabetic Clin., Beth Israel Hospital, Boston, Mass.*): SOME EMOTIONAL ASPECTS OF THE TREATMENT OF DIABETES MELLITUS AND THE ROLE OF THE PHYSICIAN. New England J. Med. 249:471-76, Sept. 17, 1953.

The author describes some of the emotional aspects of the patient with diabetes mellitus during treatment and describes fourteen case histories illustrating the various points. He described many of the emotional problems which the new diabetic patient encounters and made constructive suggestions regarding how they should be handled.

Steinberg, Arthur G. (*Children's Cancer Res. Found., Children's Med. Center, Boston, Mass.*): HEREDITY AND DIABETES. Eugenics Quarterly 2:26-30, March 1955.

Investigations based on large numbers of carefully collected histories show that diabetes is about twice as frequent among the sibs (sisters and brothers) of diabetic patients who have a diabetic parent as among the sibs of diabetic patients who do not have an affected parent. Susceptibility to diabetes is inherited via a simple recessive gene which shall be symbolized as "d." *Individuals who are genetically liable to diabetes are indicated as "dd." Those not genetically liable to diabetes are "Dd" or "DD."* Estimates based on two different sets of data indicate that about 5 per cent of the population of the United States is homozygous for the gene determining susceptibility of diabetes, that is, are "dd." As a consequence of the variability in age at onset and in the severity of the disease, only about 1 per cent of the population is recognized to be diabetic. It appears from various studies that an additional 1 per cent of the population is diabetic but not recognized to be so. It is concluded, therefore, that 60 to 80 per cent of those who are genetically liable to diabetes, that is, who are "dd," are not recognized by present routine methods of examination.

It has been claimed that, on the average, diabetes will occur in the child of a diabetic at an age twenty years lower than that at which it occurred in the parent and that the child is no longer liable to diabetes when it has passed the age at which the parent became diabetic. This phenomenon is referred to as anticipation. About two-thirds of diabetic patients with a diabetic parent develop their diabetes at an earlier age than the parent. Analysis of such data, however, has shown that there is no causal relationship between the age at onset of diabetes in parent and child. Hence, there is no reason to believe that a child is no longer liable to diabetes when he has passed the age at onset of his diabetic parent. On the contrary, the risk may be quite high if the parent was young when he became diabetic. It is concluded that at the present time there is no method of predicting when a person who is genetically liable to diabetes will be diabetic.

Strang, Christopher; and Walton, John N. (*Dept. of Med., Royal Victoria Infirmary, Newcastle upon Tyne, England*): CARCINOMA OF BODY AND TAIL OF PANCREAS. Ann. Int. Med. 39:15-37, July 1953.

Fifty-eight cases of carcinoma of the body and/or tail of the pancreas are reported; the diagnosis was made at laparotomy in thirty-seven cases, at autopsy in twenty-one. The condition occurred approximately once in every 6,000 admissions to the hospital over a twenty-year period. The incidence of the cases coming to post-mortem was 2.3 per thousand autopsies. Forty of the patients were male (69 per cent), eighteen female (31 per cent); the average age was 56.8 years. The primary growth was situated in the body of the organ in thirty-four cases, in the body infiltrating the head in five, and in the body and tail in fourteen, and in the tail in five.

Symptoms had been present for an average of four and one-half months before admission, and in thirty cases the average total duration of the illness was seven to eight months. Diabetes mellitus occurred in one case only. The clinical diagnosis was correct in only three cases, and although intra-abdominal malignancy was suspected in many, numerous other diagnoses were suggested. Study of the pathologic findings did not suggest that the clinical picture varied significantly with the situation of the neoplasm within the pancreas.

Metastasis occurred most commonly to regional lymph nodes, liver omentum, gastrointestinal tract, adrenals and bones, but many other organs were occasionally involved. Multiple vascular thrombi were noted in five of the autopsied cases (24 per cent).

It is concluded that in the presence of the clinical features described, and even if multiple investigations are negative, laparotomy may be indicated. In many cases, the primary growth will be inoperable before significant symptoms appear, but in others laparotomy on suspicion may confirm the diagnosis and lead to successful treatment.

Sunderman, F. William (*Div. of Metabolic Res., Jefferson Med. Coll., Philadelphia, Pa.*): FURTHER MODIFICATIONS IN THE MEASUREMENT OF BLOOD GLUCOSE.

Am. J. Clin. Path. *23*:193-96, February 1953.

A micro adaptation of the Sunderman-Fuller procedure for estimating blood glucose has been described. A new tube has been designed for use with both the macro and micro procedures for estimating blood glucose and for use with either visual or photoelectric colorimetry.

Thiele, O. W.; and Bohn, H. (*Medizinischen und Nervenklinik der Justus Liebig-Hochschule Giessen*): TREATMENT OF DIABETES MELLITUS WITH COCARBOXYLASE. THE RELATIONSHIPS TO CREATINE METABOLISM. Klin. Wchnschr. *32*:815-17, Sept. 1, 1954.

When cocarboxylase was administered to diabetics with creatinuria there was no creatine elimination for two days in the twenty-three cases, while the total creatinine elimination and the pyroracemic acid concentration in the blood remained unchanged. Cocarboxylase probably acts as a phosphoric acid donator so that the phosphorylation function of creatine phosphoric acid is relieved, the latter therefore no longer dephosphorylates intensively, and thus creatine is no longer eliminated in the urine. In cases of diabetic coma, the greatly increased pyroracemic acid level drops with progressing recovery to slightly increased values, independent of the method of treatment (insulin or insulin+cocarboxylase). (German)

Thosteson, George C. (*Harper Hosp., Detroit, Mich.*): DIABETES AND PREGNANCY. Harper Hosp. Bull. *11*: 245-47, November-December 1953.

Primiparae and multiparae with short duration diabetes may be candidates for vaginal delivery where there are no obstetrical contraindications and the conditions for induction appear suitable. Patients with diabetes of over five years' duration are candidates for elective cesarean section. The results with hormonal therapy were inconsistent and unimpressive. Factors assuring the diabetic patient a successful gestation appear to be adequate control of diabetes and careful timing of delivery, accomplished through the close co-operation of internist, obstetrician and pediatrician.

Thunberg, Torsten (*Physiol. Inst., Univ. of Lund, Lund, Sweden*): OCCURRENCE AND SIGNIFICANCE OF CITRIC ACID IN THE ANIMAL ORGANISM. Physiol. Rev. *33*:1-12, January 1953.

The position of citric acid as a metabolite is to a large extent the same as that of a simple sugar. It is completely consumed in the animal organism, its combustion value being 2.47 calories per gm. As much as 30 or 40 gm. per day of citric acid from food is utilized in man especially from milk, potatoes, and green vegetables. Citric acid is of general importance in metabolism owing to its connection with the complicated enzyme system, the "citric acid cycle," which forms a connecting link between the three main metabolic pathways for complete oxidation of carbohydrate, fat, and protein. The rich amount of citric acid in bone raises the question of whether citric acid has any mechanical function, for example, as a cement substance. Citric acid's substantial occurrence in semen indicates that it has some as yet not fully understood importance in reproduction. The chemical properties of citric acid, particularly its affinity for calcium (and magnesium) and its widespread occurrence in tissues and fluids, are such that it affects cell permeability and the irritability of the nervous system.

Volk, Bruno W.; Lazarus, Sydney S.; and Goldner, Martin G. (*Div. of Labs. and Dept. of Med., Jewish Chronic Disease Hospital, Brooklyn, N. Y.*): ALPHA CELL DAMAGE AND BLOOD SUGAR CHANGES IN RABBITS AFTER ADMINISTRATION OF COBALT. Proc. Soc. Exper. Biol. & Med. *82*:406-11, March 1953.

Cobaltous chloride in varying doses was administered intravenously to normal and alloxan diabetic rabbits. Doses between 40 and 50 mg. produced most consistent rises in blood sugar and histologic changes in the alpha cells of the pancreas, while doses of 100 mg. or more proved to be toxic. A single injection of 50 mg. was accompanied by transient hyperglycemia and rapid selective injury to the alpha cells which was still present after ten days, with regeneration beginning by the sixth day. Repeated injections of cobaltous chloride in the same animal produced the same hyperglycemia irrespective of the anatomic changes present in the alpha cells. In the alloxanized animal, each injection was followed immediately by an augmentation of the hyperglycemia which was more prolonged but of the same degree as in the normal; after the second or third cobalt injection in some animals the fasting blood sugar gradually fell but after four or five days returned to the precobalt level, despite the fact that alpha-cell damage was still present. The authors conclude that the effect on blood sugar level of cobalt is due to an extrapancreatic toxic action, probably on the liver, and that the severity of the diabetes of the alloxanized animal is not the result of a physiologic hyperglycemic action of the alpha cells.

Volk, Bruno W.; Lazarus, Sydney S.; Lew, Herbert (*Div. of Labs., Jewish Chronic Disease Hosp., Brooklyn, N. Y.*): EFFECT OF VARIOUS HORMONES ON THE RATE OF DECLINE OF THE BLOOD SUGAR IN THE MODI-

FIED GLUCOSE INSULIN TOLERANCE TEST. Metabolism 4:10-17, January 1955.

The modified glucose-insulin tolerance test consists of intravenous injection of 25 gm. of glucose in 50 per cent solution, followed in thirty minutes by 0.1 units of crystalline insulin per kilogram of body weight. The test was used to evaluate the effect of various hormones on the rate of decline of the blood sugar concentration in animal experiments. The mean value of the rate of decline of the blood sugar from thirty minutes to sixty minutes after glucose for the normal dog is 2.9 mg. per 100 ml. per minute with a standard deviation of 0.6 mg. per 100 ml. per minute. The dogs rendered insulin insensitive with growth hormone, corticotropin, cortisone and hydrocortisone, and alloxanized cobalt-treated animals had values of less than 2.3 mg. per 100 ml. A rapid rate of decline, signifying insulin sensitivity was noted in the adrenalectomized, hypophysectomized and alloxanized animals following the modified glucose-insulin tolerance test.

Walter, A. B. (*Lancaster Hosp., Lancaster, N. B.*): DIABETES MELLITUS—AN EXCEPTIONAL CASE. Canad. M.A.J. 72:297-98, Feb. 15, 1955.

An interesting case is presented which describes a patient who developed diabetes and dry gangrene of three toes at the age of fifty-six. He was well and healthy after twenty-two years of self treatment, which included twice daily regular insulin injections without sterilization of needles or syringes and amputation of one of his own toes.

Ward, L. Emmerson; Polley, Howard F.; Slocumb, Charles H.; Hench, Philip S.; Mason, Harold L.; Mattox, Vernon R.; Power, Marschelle H. (*Depts. of Med. & Biochem., Mayo Clin., Rochester, Minn.*): THE EFFECTS OF ALDOSTERONE (ELECTROCORTIN) AND OF 9α FLUOROHYDROCORTISONE ACETATE ON RHEUMATOID ARTHRITIS: PRELIMINARY REPORT. Proc. Staff. Meet., Mayo Clin. 29:649-63, Dec. 22, 1954.

Aldosterone, an adrenocortical hormone, produced no significant alteration in carbohydrate metabolism in two cases of rheumatoid arthritis. In cases of Addison's disease, aldosterone may bring towards normal blood sugar values and glucose tolerance curves which are relatively hypoglycemic.

9α-fluorohydrocortisone showed little alteration in carbohydrate metabolism during a short treatment period in four cases.

Weiner, Aaron (*Brooklyn, N. Y.*): SITUS INVERSUS WITH DIABETES MELLITUS AND PERNICIOUS ANEMIA. New York State J. Med. 52:1321-22, May 15, 1952.

A case report.

Weinstein, Paul: THE SIGNIFICANCE OF DIABETIC RETINITIS. Ophthalmologica 121:353-56, June 1951 (Abstr. in Am. J. Ophth. 35:296, February 1952).

The systemic findings in thirty cases of diabetic retinopathy are reported. There was a high incidence of high capillary fragility, of abnormalities of the electrocardiogram and, in the cases of retinitis proliferans, of low creatinine clearance.

Wick, Arne N.; and Drury, Douglas R. (*Scripps Metabolic Clin., La Jolla, and Dept. of Physiol., Univ. of Southern California, Los Angeles, Calif.*): INFLUENCE OF GLUCOSE CONCENTRATION ON THE ACTION OF INSULIN. Am. J. Physiol. 174:445-47, September 1953.

The effect of plasma glucose concentration on the rate of glucose disappearance and oxidation has been determined in the extrahepatic tissues of insulinized rabbits, using radioactive glucose in the study. A ten-fold increase in glucose concentration produces a two-fold increase in transfer rate from the plasma into the cells. The oxidation of glucose parallels the glucose disappearance rate, probably due to the increased amount of glucose transferred intracellularly. These results are consistent with the view that the nature of insulin action is to promote the transfer of glucose from the extracellular fluid into the cell and the disposition of such glucose depends on other factors within the cell.

Wick, Arne N.; Morita, Toshiko N.; and Barnet, Harry N. (*Scripps Metabolic Clin., La Jolla, Calif.*): SORBITOL METABOLISM IN ALLOXAN-DIABETIC ANIMALS AS COMPARED WITH FRUCTOSE AND GLUCOSE. Food Res. 20: 66-70, January-February 1955.

The oxidation of sorbitol, fructose, and glucose has been examined in alloxan-diabetic rats. When the animals are placed on a 68 per cent sucrose diet, approximately 50 per cent of the administered sorbitol and fructose carbon is recovered in the expired air, whereas for glucose 26 per cent is recovered. When the animals are maintained on a 68 per cent fructose diet, fructose is no better oxidized than glucose, but the oxidation of sorbitol is not reduced. These results have been used to support the view that at least two pathways exist for the oxidation of sorbitol or fructose. An evaluation of the relative participation of sorbitol and fructose by these pathways is discussed.

Wolff, H. (*Munich, Germany*): ON THE NATURE AND CLINICAL BEHAVIOUR OF SERUM ZINC. Verhandl. deutsch. Gesellsch. inn. Med. 58:461-63, 1952.

The zinc distribution in the pancreas is characterized by a selective concentration of this metal in the β-cells. In the serum, the zinc content varies between 120 and

170 gamma per cent. About 60 per cent of the serum zinc is bound to albumin, the rest to globulins. The zinc of the albumin fraction is dialysable, and it seems that this is the fraction of the serum zinc which varies under pathological conditions. The albumin zinc is the transport form of the serum zinc, while the globulin-bound zinc is more stable.

The serum zinc was studied in almost 200 cases of different internal diseases. During fever, serum zinc is inversely proportional to the body temperature. This is especially impressive in cases of lobar pneumonia. At the height of the disease, it is about 30 to 40 per cent lower, and it returns to normal values with the clinical improvement of the patient. Characteristic lowering of serum zinc was found in parenchymal alterations of the liver or the kidneys, in cases of malignant tumors, chronic polyarthritis, leukemias, and pernicious anemia. In acute conditions, the zinc values return to normal parallel with the improvement of the patient, but in chronic and irreparable changes they remain lowered.

In pernicious anemia, serum zinc is reduced, but the zinc of the erythrocytes is increased 100 to 300 per cent. The increase is due to a considerable increase of the zinc containing carboanhydrase. Under the influence of therapy with vitamin B_{12}, serum and erythrocyte zinc return to normal values. With albuminuria, an increased elimination of zinc through the urine is always observed; this parallels the loss of protein. (German)

Zanca, Ralph (*Med. Serv., Central Maine Gen. Hosp., Lewiston, Me.*): THE MANAGEMENT OF PERIPHERAL VASCULAR DISEASE IN DIABETICS. J. Maine M. A. *46*: 68-70, March 1955.

The most important problem in the management of diabetics has become the treatment of arteriosclerosis involving chiefly the coronary and the leg arteries.

The type of vascular lesion encountered in diabetics is atherosclerosis of the larger arteries and a fibrinous hyperplasia of the intima, even to the point of occlusion of the lumen in the smaller arteries. The latter is the type of lesion that leads to diabetic gangrene.

Physical procedures such as the application of heat in an ischemic limb is a dangerous procedure and is to be avoided at all times. The ischemic limb is best kept in a slightly dependent position since the blood flow is greater than when the limb is horizontal. Passive rather than active intermittent dependency is preferred, since muscular activity in a limb increases the utilization and need for oxygen. Intermittent venous occlusion is of no value in the treatment of ischemia since it retards blood flow. The use of various vasodilator drugs and their limitations is discussed. The most important fact noted was that pain and fear could prevent any of the vasodilators from being effective in obliterative vascular disease.

The author advises the use of sympathectomy early in the course of the disease, since the poor results from this procedure are found in patients with threatened or actual necrosis.

Zimmerman, Hyman J.; Thomas, Lawrence J.; and Scherr, Edward H. (*V.A. Hosp., Omaha, Neb., and Gallinger Municipal Hosp., Washington, D. C.*): FASTING BLOOD SUGAR IN HEPATIC DISEASE WITH REFERENCE TO INFREQUENCY OF HYPOGLYCEMIA. A.M.A. Arch. Int. Med. *91*:577-84, May 1953.

The level of the fasting blood sugar was studied in a large group of patients with hepatic disease including cirrhosis, infectious hepatitis, metastatic carcinoma, and toxic hepatitis, as well as in four patients with primary carcinoma of the liver. Values below 60 mg. per 100 cc. were found in approximately 2 per cent of the patients, while values below 50 mg. per 100 cc. were present in 1 per cent of the entire group. No correlation could be established between the height of the fasting blood sugar and the degree of sulfobromophthalein (bromsulfalein) retention, serum bilirubin elevation, or the magnitude of blood sugar rise after the administration of epinephrine. Hepatic disease is infrequently complicated by fasting hypoglycemia. Nevertheless, when spontaneous hypoglycemia occurs, disease of the liver should be considered in the differential diagnosis.

EDITORIALS

ANSWERING THE CHALLENGE OF DIABETES: THE NEW YORK DIABETES ASSOCIATION, A PIONEER AFFILIATE

Nineteen fifty-four marked the twentieth anniversary of the organized campaign against diabetes in New York City. It was the day after Christmas of 1934 that the New York Diabetes Association was founded. The prime movers were a small group of physicians and public health workers who approached the problem with constructive imagination. Two former presidents of the Association, the late Dr. Herman O. Mosenthal and the late Dr. Charles Bolduan were the guiding spirits.

What the Association has done in advancing diabetes control, as well as the developments that lie ahead, are here reviewed. In starting this campaign two decades ago, the Association helped lead the way to the recognition of diabetes as a public health problem. Today, there is an American Diabetes Association with nearly forty local affiliates throughout the country. There are also 850 committees organized within medical societies which are working to find the individuals with undiagnosed diabetes, and bring them to medical treatment. The United States Public Health Service and some city and state health departments have incorporated diabetes control as an important aspect of their programs. The fight against diabetes has come of age. But this disease is a perennial foe and the years ahead must bring an intensified attack.

From its inception, the New York Diabetes Association has directed its efforts toward professional and lay education, emphasized research and made facilities available for diabetic patients. An important phase of the latter has been the operation of a summer camp, to provide vacations for diabetic children and at the same time demonstrate that a diabetic can live a full life.

During its first three years the Association was an affiliate of the New York Tuberculosis and Health Association. In 1938 it became independent and incorporated as a nonprofit membership agency. A Clinical Society, the professional arm of the Association, was created in 1944, and two years later a Lay Society was organized to interest patients and the general public in its work.

At present its strength is derived from the following groups all of whom serve on a voluntary basis:

1. An active Board of Directors composed of physicians and public-spirited lay men and women. 2. An advisory Council of distinguished citizens who act as consultants for the Association. 3. A Clinical Society made up of physicians and scientific workers, which has the responsibility for the professional program. 4. A Lay Society of patients and other interested laymen which carries on the nonprofessional work of the Association. 5. A Camp Committee which directs the operation of the summer camp. 6. A Camp Service group, which helps raise funds for the camp.

The Association is an Affiliate of the American Diabetes Association, receives support from the Greater New York Fund, is a member of the Welfare and Health Council of New York City, and works in close cooperation with the County Medical Societies, the New York Academy of Medicine, the New York City Health Department and other public and voluntary health and welfare agencies.

Its annual budget amounts to $70,000 of which $55,000 goes towards the operation of the summer camp NYDA. Only about 4 per cent is spent for direct fund raising. Its office staff numbers three permanent employees.

TWENTY YEARS OF PROGRESS

The Association's major activities comprise the following:

1. *Professional Education*

No public health activity has ever been successful without a well-planned program of professional education.

To meet this need the Association's Clinical Society has conducted educational programs for physicians including lectures, seminars, conferences, and round table

An abridgment of the Report of the President to the Board of Directors of the New York Diabetes Association, Inc., Nov. 9, 1954.

discussions on various aspects of diabetes. Several series of articles and helpful booklets on modern concepts of diagnosis and treatment have been made available to the medical profession. Scientific exhibits have been displayed at the Graduate Fortnight of the Academy of Medicine and at other conventions devoted to medicine and public health.

To promote active collaboration between internists treating diabetes and specialists in other diseases in which diabetes plays a role, cooperative meetings have been arranged with sections of the New York Academy of Medicine and other local specialized medical organizations.

To promote improved standards of patient care in the more than seventy diabetes dispensaries operating in the city, a program to standardize clinical procedures was inaugurated. Thus, systematic efforts have been made to secure acceptance by dispensaries of the methods of meal planning and food exchanges described in the *Diabetes Guide Book for the Physician* of the American Diabetes Association as a basis for diet prescription. When generally adopted, it will constitute an important contribution to the welfare of the diabetic patient.

2. *Research*

When the Association was founded, organized research in the field of diabetes was entering a new phase. Any modest grants that the Association could award to research were parcelled out to the hospitals. These sums were too small to make much impact. The Association, therefore, is now devoting its relatively small funds to bringing knowledge of research to the attention of the medical profession.

A *Symposium on Diabetes* was held on Oct. 8, 1953, and again on Oct. 14, 1954. Distinguished scientists and clinicians presented authoritative summaries and reviews of current research in the field of diabetes and general metabolism and their application to the general practice of medicine.

3. *Public Education*

Unfortunately, large numbers of people still are not sufficiently aware of the success of modern treatment of diabetes or of the great dangers from delay in diagnosis and treatment, or from relying upon "quacks." During the first twenty years, the Association has used several educational media to acquaint the public with facts about the disease in the hope that they would seek medical treatment promptly.

Intensive popular educational campaigns have been conducted in cooperation with the New York City Health Department, the Health Council, and County Medical Societies. Radio talks have been broadcast and lectures given by physicians before social, civic, health and welfare groups. Informative literature has been distributed and popular exhibits displayed in strategic locations. The message has reached thousands of homes through leaflets, articles in the press and poster displays in drug stores and motion picture houses.

The New York Diabetes Association has cooperated with the American Diabetes Association and the County Medical Societies in the annual Diabetes Detection Drive. The Clinical Society's Committee on Diabetic Detection and Lay Education has been developing a program to enable industrial and commercial firms to set up diabetes detection screening projects for their employees.

4. *Camp* NYDA

During the past eighteen years, Camp NYDA, located since 1946 on the Association's forty-acre property in the Shawangunk Mountains, has provided summer vacations for over 1,000 diabetic children. The Camp is supported by voluntary contributions, and no child is refused admission because of inability to pay.

Under medical supervision and with the aid of experienced educators, the young diabetics learn how to care for themselves. They are taught the proper value of food and nutrition, how to test their own urine, and how to administer insulin. Normal life and camp activities are stressed. Happy as well as healthy children is the aim.

The increased publicity received by the Camp has presented the Association with the problem of a large waiting list. As a partial solution, beginning with 1954, the camp will accommodate three groups of eighty children each for three weeks instead of the previous four-week period for two groups of eighty children. This makes it possible to give vacations to 240 children instead of 160.

5. *Other Activities*

Those suffering from diabetes are often mistakenly looked upon as chronic invalids and excluded from jobs and other activities they could perform competently without handicap or hazard. The Association, through its Lay Society, has tackled such difficult problems as insurability and employment for diabetics. Support has been enlisted from prominent and successful persons who are diabetics in order to show the public that the disease does not bar great achievement.

Through its Information Service, the Association has answered inquiries received from the general public and professional persons.

The influence of the Association has been more than local. In 1939, it helped promote plans for the establishment of the American Diabetes Association.

LOOKING AHEAD

This brief summary of the past twenty years indicates that the Association is playing an important part in the control of diabetes. But the Association needs more financial resources in order to carry out its functions adequately. Its educational work must be intensified, a systematic program of patient education must be developed, the facilities at Camp NYDA must be expanded, and there is need for statistical analysis of the effects of the various newer forms of therapy.

HERBERT POLLACK, M.D.
New York

"IN THE INTEREST OF DOCTOR AND PATIENT"

"Your Council voted to establish the Banting Medal to be given to the retiring President and Banting Memorial Lecturer. This procedure is to be made retroactive."

This statement appears on page thirty-six of the *Proceedings* of the American Diabetes Association for 1944, in the "Report of the Secretary" by Cecil Striker, M.D.

The motion to establish the Banting Medal was passed at the Council Meeting held Feb. 19, 1944. It had been introduced upon the instigation of Joseph H. Barach, M.D., one of the founders of the Association and its President for the years 1944-46. In addition to being given to the Presidents and the Banting Memorial Lecturers, the medals may, in Dr. Barach's words, "also be presented as the occasions arise to other distinguished members of the profession who have made notable contributions to the knowledge of diabetes."

Soon after the striking of the medal was authorized, Dr. Barach prepared design sketches for it which were based on a composite of photographs of Banting, made at various times by his late cousin and life-long companion, Dr. Frederick W. Hipwell. From these sketches, the actual medal was executed by the talented sculptor, A. Paoli, of New York, and Summit, New Jersey. Paoli's personal interest in this commission, which was made possible by Dr. Barach's own generosity, produced a medal that is much more than a faithful reproduction.

When the original of the medal was shown to the members of the Council, practically all of whom had known Banting personally for years, it met with instant admiration and approval. The original, a large bronze casting made direct from the sculptor's mold, was presented by the American Diabetes Association to the University of Toronto on the occasion of the celebration of the twenty-fifth anniversary of the discovery of insulin by Banting and Best, which took place at Toronto in 1946. At the same time smaller reproductions of the medal were presented to the honored guests of the Association at that anniversary celebration, Drs. Bernardo A. Houssay, of Argentina; H. C. Hagedorn, of Denmark; R. D. Lawrence, of England; and Eugene Opie, of the United States.

THE BANTING MEDAL

Each year thereafter the Banting Medal has been presented at the Annual Meetings of the Association to its retiring Presidents, and to its Banting Memorial Lecturers. It is also awarded on occasion to others "For Service in the Field of Diabetes." By now it has become the honored symbol of the American Diabetes Association, and an award much treasured by its recipients.

Since the institution of Banting Medals they have been presented to these distinguished physicians and scientists:

Banting Memorial Lecturers

1941 Elliott P. Joslin, M.D.
1942 William Muhlberg, M.D.
1943 Frederick W. Hipwell, M.D.
1944 Leonard G. Rowntree, M.D.
1947 G. H. A. Clowes, M.D.

1948	Rollin T. Woodyatt, M.D.
1949	Herbert M. Evans, M.D.
1950	F. G. Young, D.Sc.
1951	C. N. H. Long, M.D.
1952	Charles H. Best, M.D.*
1953	Shields Warren, M.D.
1954	Sir Henry Dale
1955	Carl F. Cori, M.D.

Presidents of the American Diabetes Association

1941	Cecil Striker, M.D.
1942	Herman O. Mosenthal, M.D.
1944	Joseph T. Beardwood, Jr., M.D.
1946	Joseph H. Barach, M.D.
1947	Russell M. Wilder, M.D.

*A special plaque was presented to Dr. Best as he previously had been awarded the Banting Medal as a retiring President.

1948	Edward S. Dillon, M.D.
1949	Charles H. Best, M.D.
1950	Howard F. Root, M.D.
1951	Lester J. Palmer, M.D.
1952	Arthur R. Colwell, M.D.
1953	Frank N. Allan, M.D.
1954	Randall G. Sprague, M.D.
1955	Henry B. Mulholland, M.D.

Medalists selected "For Service in the Field of Diabetes"

1946	Bernardo A. Houssay, M.D.
1946	H. C. Hagedorn, M.D.
1946	R. D. Lawrence, M.D.
1946	Eugene Opie, M.D.
1949	Frederick M. Allen, M.D.
1952	Prof. R. R. Bensley
1953	Walter R. Campbell, M.D.
1953	A. Almon Fletcher, M.D.
1955	Eugene F. DuBois, M.D.

A Definition of Diabetes Mellitus

Diabetes mellitus is a metabolic disorder of endocrine origin. It primarily involves carbohydrate metabolism but also affects the metabolism of protein, fat and minerals. It results from a deficiency, either absolute or relative in the supply of insulin from the islands of the pancreas. This deficiency, however, may be modified by the activity of other endocrine organs (including the pituitary, the adrenals, the thyroid and the liver). The disorder is manifested by hyperglycemia and glycosuria and tends to lead to malnutrition, ketoacidosis and complications affecting the arteries, peripheral nerves, eyes and kidneys.

By Frank N. Allan, M.D., in *Internal Medicine, Its Theory and Practice,* originally edited by John H. Musser, M.D., 5th edition by Michael G. Wohl, M.D., Philadelphia, Lea and Febiger, 1951, p. 514.

Robert R. Bensley

Henry T. Ricketts, M.D., Chicago*

More than forty years ago Dr. Robert R. Bensley, then Professor of Anatomy at the University of Chicago, provided one of the important links in the discovery of insulin by showing that the islands of Langerhans comprise an organ system distinct in both structure and function from the acinar cells of the pancreas. By students of diabetes, this, and his demonstration of the differential staining properties of the alpha and beta cells, will be regarded as outstanding among his many contributions.

Dr. Bensley was born on a farm south of Hamilton, Ontario, in 1867. His father was English and his mother Irish. After a few years in a country school he pursued his education in Hamilton and then at the University of Toronto, where an earlier interest in languages gave way to science. In his third year at college, at the age of twenty, he suffered a severe gunshot wound of a leg, resulting in thrombophlebitis, septicemia, gangrene and eventual amputation. This illness cost him a full year, but it will surprise no one to learn that the year was not all wasted. His father bought him a microtome and Bensley spent his time learning histologic technics and experimenting with the staining of sections, including wood chips, with "diamond" dyes.

In 1892 he graduated from the medical school of the University of Toronto, having taught histology while still a student. The same year he married Carriella May and, while continuing his teaching at the University, began the practice of medicine. He also found time for investigation, and during this period worked out the microchemical reaction for mass iron, subsequently known as the McCallum reaction. "It's no good," he says of it today.

Among Dr. Bensley's early research interests was the histology of the gastrointestinal tract. A paper on this subject, published in 1896, established the identity of the neck chief cells of the gastric mucosa, and another, in 1902, carried the demonstration that the glands of Brunner in the duodenum are derived from the pyloric glands of the stomach.

In 1901 he accepted a post in the Department of Anatomy at the University of Chicago. It was soon after this that he became interested in the pancreas as a result of publications from Starling's laboratory purporting to show that the islets, instead of having an identity of their own, are part and parcel of the acinar system and that the cells of both are mutually interconvertible. Some of the observations cited by the British workers in support of their theory consisted of the counting of islets in small sections of pancreas before and after stimulation with secretin, a substance known to increase acinar activity. It was reported that this procedure caused a definitive increase in the number of islets, and these diminished when the pancreas was at rest.

*Professor of Medicine, University of Chicago, School of Medicine, Chicago, Illinois.

It was Bensley's opinion that such evidence was inadequate, that quantitative estimates of islet tissue based upon the examination of tiny fragments of pancreas were inaccurate, and that, moreover, the morphology of the islets and the arrangement of their blood supply, far from suggesting any exocrine function, argued strongly in favor of endocrine activity.

In order to determine not who was right but what was true, to use Bensley's own aphorism, new tools were needed, and these he supplied. He devised a method of supravital staining with janus green and other dyes which permitted him to do three things. First, it allowed him to stain all the islets in the entire pancreas of the guinea pig and hence to enumerate them accurately rather than relying upon estimations and calculations derived from small bits of tissue. Thus he was enabled to show conclusively that agents such as secretin and starvation, which do affect the acinar cells, have no influence on the number of islets. Second, it permitted the demonstration that the islets, while derived from the duct system and often more or less loosely connected with it, have no egress into it through any hollow structures, and hence can have no excretory function. Third, by the development of specific granule stains he was able to show that the alpha and beta cells retain their identity through various phases of acinar activity, with no evidence of transition into or out of the cells of the acini. Bensley's granule stains have since been widely used in investigating the physiology and pathology of the islet cells themselves.

By these classical studies, published in the *American Journal of Anatomy* in 1911, Bensley firmly established the islet system as an independent entity whose structure and relationships seemed designed for internal secretion. By so doing, he promoted in large measure the understanding of the islets that was to lead eventually to the work of Banting and Best.

While the cytology of the islets continued to interest Dr. Bensley and his later students, particularly Lazarow, Woerner and Sylvia Holton, Bensley's curiosity ranged over many other fields. In 1910 he placed the existence of the Golgi apparatus on a solid footing. In 1912, with B. C. H. Harvey, he published the results of investigations on the mechanism of hydrochloric acid secretion in the stomach, and three years later demonstrated histologically the intracellular precursor of the secretion of the thyroid.

As the years passed he devoted himself increasingly to the fundamentals of cytology and histochemistry. The minute structure of the cell intrigued him, and to this problem he brought, in his own person, the diverse talents of the chemist, pathologist, physician and connoisseur of nature. To these were added the qualities of imagination tempered by objectivity and perserverance supported by enthusiasm. Small wonder, then, that in 1934, after nearly thirty years of study and effort, and one year after his official retirement, he finally succeeded in separating the mitochondria of liver cells in pure form and subjecting them to chemical analysis. Since that time he and his students, using new technics, some of his own invention, have done much to elucidate the structure and chemical composition of cytoplasm.

In 1952, Dr. Bensley was presented with the Banting Medal of the American Diabetes Association. He was also elected to honorary membership in the Association.

Hard by the University that he has graced for many years (Bensley, a life-long hunter and fisherman, might say within rifle shot, which about describes it), he lives in a modest dwelling with his daughter, Caroline May. His easy chair in the living room is surrounded by a clutter of papers and scientific journals, a testimony, if any were needed, to the persisting activity of his mind and the breadth of his interests. Those who knew him in earlier years would today miss none of the forthrightness of opinion, the directness of expression, the retentiveness of memory or the pungency of his humor that have always marked his relationships with his colleagues and his numerous students. Nor has he lost the ability to evaluate fairly, neither with boasting nor false humility, his own contributions. His physical ills he still bears, at the age of eighty-seven, with the philosophy and objectivity of a scientist. His rich life, past and present, is the kind any man would like to have lived for his own.

Organization Section

Address of the President

Henry B. Mulholland, M.D., Charlottesville, Virginia

For some months, I have given considerable thought to the subject matter of this, my farewell address as your President. The events of the past year have suggested that this may be the appropriate time to indulge in a little self-analysis, briefly taking a look into the past. This will give us an opportunity to take stock of our major accomplishments up to the present. Then we shall endeavor to project ourselves into the future, to predict as well as we may the direction our course should take.

A week from tomorrow—June 12th—will mark the fifteenth anniversary of the founding of the American Diabetes Association. During these fifteen years, it is fair to state that we have passed the period of adolescence and have begun to mature.

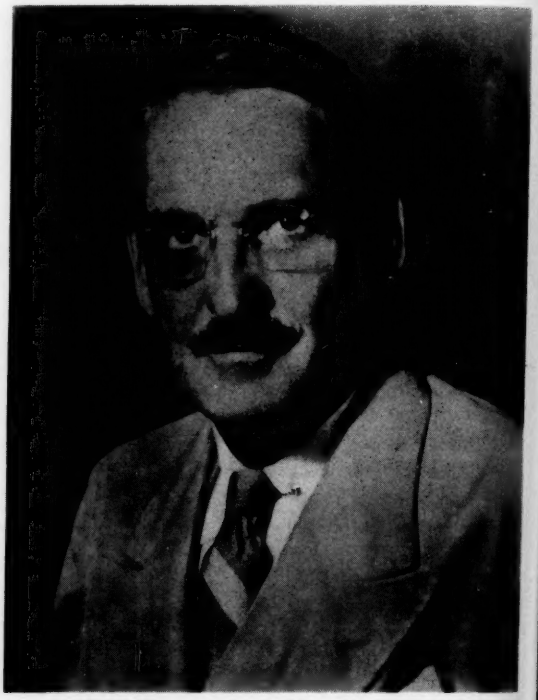
Because there are so few in the audience who participated at the birth of our organization, it might be appropriate to relate to our present members a few interesting highlights in connection with its origin.

At a meeting of the American College of Physicians three years before the Association was founded, an interested group of physicians discussed the idea of forming a national diabetes association. Nothing happened for about a year. After a considerable amount of correspondence between those who were present at the original meeting—particularly between Cecil Striker and the late Herman O. Mosenthal—it was agreed that the first step was to invite the cooperation of existing local diabetes groups, of which there were then only five.

It seemed perfectly natural at that time that the idea of a group of physicians associating themselves because of their mutual interest in diabetes should evolve from a discussion of difficulties in evaluating an insulin preparation.

The original group of men, together with twelve representatives of the known local diabetes organizations, met in Cleveland in April of 1940. Cecil Striker presided as Chairman of that meeting, which was attended by the late Herman O. Mosenthal, who acted as Secretary, Samuel Altschuler, Joseph T. Beardwood, Jr., the late Charles F. Bolduan, C. F. F. Gibbs, Louis B. Owens,

Delivered at the Banquet, 15th Annual Meeting, Atlantic City, New Jersey, June 4, 1955.



HENRY B. MULHOLLAND, M.D., PRESIDENT, 1954-55

Dr. Mulholland was born in Knoxville, Tennessee, in 1892. He started his medical education at the University of Toronto and transferred to the University of Virginia Medical School where he graduated in 1920. At the present time he is Assistant Dean and Professor of Internal Medicine of that institution.

Dr. Mulholland was one of the first members of the American Diabetes Association, and a Councilor since 1947. He has been Chairman of many Association Committees including Emergency Medical Care, Scientific Programs and Scientific Exhibits. He became a Vice President in 1952, and has served as President during the past year.

Dr. Mulholland has served as a Consultant to the government and a member of Commissions on many occasions. Likewise, he has long been active in the American Medical Association and other medical organizations.

William S. Reveno, Laurence F. Segar, George C. Thosteson, J. L. Tuechter and Frederick W. Williams.

As many of you know, Cecil Striker became the first President of our Association, and Herman Mosenthal was the second President.

It is only fitting and proper that the names of the others who attended the meeting of June 12, 1940, be mentioned: Sidney Adler, Samuel S. Altschuler, George E. Anderson, Benjamin I. Ashe, the late Joseph H. Barach, who served as President of our Association for two terms, Joseph T. Beardwood, Jr., Belford C. Blaine, the late Charles F. Bolduan, Frank B. Cross, Beeckman J. Delatour, Joseph N. Ganim, Charles M. Levin, I. Arthur Mirsky, J. West Mitchell, Paul F. Polentz, Herbert Pollack, Philipp Schmahl, James R. Scott, Beverly C. Smith, the late Anna O. Stephens, George F. Stoney, Edward Tolstoi, Millard Wallenstein, and last—but not least—Fred Williams, now serving as Second Vice President of our Association. The twenty-six physicians whose names I have just read were the original founders of our Association.

When one considers that the Association operated with a budget of around $50 a month in the beginning and that today we have more than 2,000 members with a budget of over $200,000 a year, you can fully appreciate its steady growth. As evidence of their interest in diabetes, 300 physicians attended the first Annual Meeting of the American Diabetes Association in Cleveland, June 1, 1941.

Through the broad vision and the character of the devoted men who have been Officers and Councilors, we have seen the American Diabetes Association grow from a gathering which met once a year to exchange scientific information to a group concerned with the broader aspects of diabetes, fully recognizing its responsibilities to physicians, patients and the public.

OUR EXPANDING HORIZONS

Within this enlarged horizon, we must be prepared to shoulder greater responsibilities. It is my intention to outline to you my conception of our future goals.

We should not allow ourselves to become a group of specialists concerned only with treating the condition diabetes mellitus. Primarily our main concern should be to see that our patients obtain the best possible medical care, and to this end, therefore, our objective should be to interest every general practitioner in the detection, treatment and care of the diabetic.

One of the four major principles we have adopted as members of this Association is that of professional education. Involved in this activity is the Annual Meeting like the one we are holding today, with its fine professional papers and the annual Banting Memorial Lecture. Of equal importance is the Journal DIABETES, established only three years ago but already recognized as an excellent medical periodical, containing as it does the finest abstract service of any medical journal in this field.

Started with some misgivings, the attendance at our annual postgraduate seminars has far exceeded our greatest expectations. Our Committee on Professional Education has been considering the extension of similar courses on a regional basis. However, after a survey, we are satisfied that some of our Affiliates already are fulfilling this proposed activity through local scientific meetings and discussions which are held under their guidance. With roughly 3,000 members of Clinical Societies in thirty-eight Affiliates, it is hoped that this endeavor will be carried on by them in behalf of the physicians in their areas.

The American Diabetes Association is happy to announce that a revised *Diabetes Guide Book for the Physician* will soon be on the press. This has been one of our most popular publications, and serves to present in simple fashion the diagnosis and treatment of the patient in their broadest aspects.

PROGRAM FOR PATIENT WELFARE

By far the most important and brightly shining star in our horizon is the patient, whose physical welfare is paramount. Because of this, in broadening our scope, much concern has been given to this phase of our activities.

The lay magazine, ADA FORECAST—edited, incidentally, by one of the founders of our Association, Fred Williams—is a real achievement. The magazine has over 30,000 subscribers, has a special Canadian Edition, and its contents are copied and translated by other diabetic publications in many foreign countries.

Dissemination to the diabetic of useful and accurate information through this source is vital. Another effort of great importance to diabetics and their families is the annual Detection Drive. To be sure, detection is important, but the greatest good is accomplished as a result of the widespread public interest aroused in diabetes during Diabetes Week.

Unlike other health groups, we have made no direct appeal to the public for funds. Emphasis is laid on the effort to search out those with this condition in its early stages. This is a very sound principle because, in so doing, early treatment may prevent disastrous complica-

tions later on. Even more significant perhaps are the educational aspects which sensitize the general public as well as the diabetics to the importance of diabetes and the part it plays in the welfare of the people in every community.

However, patient education does not stop there. Our National Office receives thousands of letters from diabetics and their families regarding every angle of the ailment. Many pieces of literature are sent out on their requests, and thirty-four articles which appeared in ADA FORECAST have been reprinted to meet this demand. Too much emphasis cannot be placed on the fact that we must always be on the alert to find new means and methods of enlarging our service to these individuals.

One of the most interesting developments of the past decade—insofar as our Affiliates are concerned—has been the establishment throughout the nation of diabetic camps for children. One of the latest, established in Tennessee, was made possible through the philanthropy of Mr. and Mrs. Gordon P. Street of Chattanooga, who gave $100,000 for a 360-acre tract of land on Lake Chickamauga near Soddy, Tennessee. Known as Double G. Ranch, the camp has one mile of water frontage on the lake, for canoeing and a swimming pool large enough to accommodate 120 children—twelve cabins, each built to sleep ten youngsters; innumerable buildings for the camp staff, office, storage houses and a health lodge with a ward, all built with rustic finish. Then there is a large council ring in the center of the camp for vespers, meetings, campfires and other group activities. A large athletic field is at the edge of the camp site. Double G. Ranch opens officially on July 31, with cost based on ability to pay. However, no child is to be denied the privileges of attending the camp because of inability to pay.

It takes little imagination to visualize the good that may come from giving diabetic boys and girls a chance to spend part of their vacation period as other children do, to say nothing of the tremendous importance of the educational opportunities such a gathering presents. Our Committee on Camps is now taking the leadership in formulating standards for such camps.

The American Diabetes Association's Committee on Employment is concerned with seeing that diabetics get a fair chance to compete with nondiabetics in industry, stressing the fact that most diabetics are just as competent to play their part in the national economic picture as nondiabetics.

A Committee on Therapeutic Agents and Devices has as its responsibility the consideration of any agent used in the treatment of diabetics, with its prime purpose to protect patients from nostrums and unethical methods of treatment.

BUILDING A TIGHTLY KNIT ORGANIZATION

For several years, Committees of our Organization have been working hard, and have literally burned the midnight oil, in an effort to bring about a closer tie between the National Organization and our Affiliate Associations. This group has been working with one thought in mind, namely, the mutual advantages accruing to each other through a closer relationship. I feel it is most timely and important to present to you an outline of the proposed plan together with some of the thinking behind its evolution.

Clinical Societies will continue to be the core of this revised organizational structure. In order to give each Affiliate a definite part in the National Organization picture, an Assembly of Delegates has been established. Each Affiliate selects a delegate from the Clinical Society and one delegate from the Lay Society, if the Affiliate has a Lay Society.

In addition, a Board of Governors has been formed. The National Organization appoints one Governor for each state, with certain exceptions. Each Governor acts as coordinator and adviser, within his respective state, in the entire field of diabetes and related subjects. The Board of Governors on some occasions meets jointly with our Council. The Governors also serve as the senior delegates to the Assembly of Delegates.

The Assembly of Delegates discusses such matters as it sees fit, and, in addition, considers problems which may be referred to it by our Council.

Thus, with this official tie-in with the Council, and the fact that the Councilors will have the Governors at one of their sessions, the delegates have an opportunity to participate in the formulation of policies and the business of the National Organization.

In order for this plan to work, there must be mutual respect and understanding on both sides. The American Diabetes Association expects to be of more and more real aid to its Affiliates in solving many of the problems arising out of their operations. The American Diabetes Association stands ready to aid its Affiliates in their financial drives—in fact in *any* aspect of their activities.

We shall not have sufficient time today to go into the details of the structure which we hope to set up with the Affiliates. Suffice it to say that members of Lay Societies will be given every oportunity to play an important part in the activities in their area with, of course,

the primary objective being the physical welfare of the diabetic.

It is a foregone conclusion that such a closely knit operation cannot grow up overnight. It will take time to set it up; in fact, it may be several years before we have a really sound structure. To this end, it is our sincere hope that the American Diabetes Association will eventually stand firmly upon its own feet in every way, including financial stability.

To fulfill its ultimate purpose, a health organization must have as one of its major functions the support of research in its field. Without this stimulus, its program would be sterile, lacking the spark that kindles the interest of its members. This activity is most important in the dissemination of knowledge in regard to diabetes mellitus and its problems and the addition of significant facts to their eventual solution.

The Association's Committee on Research and Fellowships, of which Charles H. Best is Chairman and Francis D. W. Lukens Vice Chairman, has been diligently at work for some time setting up such a program for this vital phase of our activities. History records that insulin was discovered through the dogged persistence of a physician, the late Sir Frederick Banting, aided by a brilliant young postgraduate student, Charles H. Best.

The American Diabetes Association firmly believes that this principle of aiding individuals is sound, and that it can best serve by helping and supporting promising young men who not only are interested in working in the field of diabetic research, but who have shown promise and ability. This year we have given two Fellowships to such individuals, and we are happy to announce that both will appear on our scientific program to report on some of their work. It is our earnest hope that—as more money accumulates for research—more of these Fellowships will become available and, to carry out the idea of support of an individual, that they may be extended over a period of several years.

To assure the ultimate achievement of our purposes and objectives, we must find the means and without too much delay. The future course of our Association may well depend on the manner in which our Affiliates respond to our request that they organize fund-raising campaigns to provide money not only for their own needs but an additional amount to help support the activities of the National Association.

During the past year more than 250 members have been appointed to various working Committees. I want to express my personal thanks to those who have served on these Committees and have given unstintingly of their time and effort to the many problems of our organization.

To remain vital and strong, we must have the deep interest and wholehearted backing of our entire membership. We must not permit the load to be carried by a few. The responsibility for the success of our Association's activities rests upon securing the full support of every member.

Perhaps it would be relevant to look back fifteen years to the time when twenty-six men founded the American Diabetes Association whose vision is fully realized here today. Their accomplishments should stimulate us now to greater efforts.

Let us always keep in mind the four major objectives of our Association—professional education, patient education, public education and case finding, and research. And let us add a fifth objective, namely, service to the patient and the public.

We definitely stand at the crossroads and the issues must be faced. In order to carry out these objectives, it is necessary that our financial structure be on a sound foundation and that the budget be balanced. Otherwise, we can do nothing but go back to an organization interested only in scientific aspects of diabetes.

To achieve these objectives, I call upon each and every member of the American Diabetes Association to rededicate himself to the principles and objectives upon which our Association was founded.

The Annual Meeting, June 4-5

THE SCIENTIFIC SESSIONS

The Program, printed in full in the March-April issue of DIABETES, attracted a large audience, the total registration numbering 580 (408 Active Members, 137 guest physicians, 35 other guests). Registration in previous years is shown in the following table:

1954	Active members	Guest physicians	Other guests	Total
San Francisco	199	99	16	314
1953				
New York	438	198	7	643
1952				
Chicago	325	102	5	432
1951				
Atlantic City	342	125	10	477
1950				
San Francisco	162	83	6	251

Sixteen scientific papers were presented, and thirteen were read by title. Two panel discussions were particularly interesting to those in attendance: "Fluids and Electrolytes in Therapy," and "What I Teach My Diabetic Patients." Participants in the first were T. S. Danowski, M.D., John E. Howard, M.D., Harvey C. Knowles, Jr., M.D., Francis D. W. Lukens, M.D., and Randall G. Sprague, M.D. The second panel included Edwin W. Gates, M.D., George M. Guest, M.D., Blair Holcomb, M.D., Elliott P. Joslin, M.D., Edwin L. Rippy, M.D., and Priscilla White, M.D.

The Banting Memorial Lecture was delivered by Carl F. Cori, M.D., Nobel Prize winner, and Professor of Biochemistry at Washington University School of Medicine, St. Louis. His subject was "The Influence of Epinephrine and Glucagon on Enzyme Systems in Liver and Muscle."

BUSINESS MEETING

The Annual Business Meeting of the Association was held June 5. The remarks of Henry B. Mulholland, M.D., President, were followed by reports of the Secretary, Executive Director, and the Chairman of the Nominating Committee.

Remarks by the President

The American Diabetes Association has been vitally concerned with many problems. We are particularly interested in our relationship with our Affiliate Associations. We hope that we can establish a closer rapport which, in the future, will bear fruit for both of us. We are also concerned with finances. Contrary to a rumor, we are not in dire straits financially merely because we are indebted to various contributors who now give us about half of our budget. However, we must look forward to the time when we may not have these generous contributors. It is because of this that we are concerned about our finances.

We are happy to announce again that we have established two Fellowships, which will begin the first of July. You have heard the recipients, Dr. John A. Owen, Jr., of Durham, N. C., and Dr. E. Rudolf Froesch, of Boston, participate in the program of this meeting. We hope to increase the number of Fellowships gradually, as money becomes available. We think this is of the greatest importance. Perhaps in the future we may also have some money for special research projects. But since funds are available throughout the country for this purpose we do not think it is necessary to go into this in a big way at present.

I should certainly like to say again how gratified we have been about the work of our Committees. This was exemplified by the attendance at the Committee meetings here. We think it is important to get as many members as we can on Committees, hoping that they will thereby take an active part in the work of the Association.

We are also pleased with the scientific program and the attendance at our Postgraduate Course. The last one, in Philadelphia, was very successful. It had 176 people enrolled and in addition many interns and residents attended.

Also, I should like to report briefly to you that we have an excellent central office; we have a wonderful Executive Director; and, in addition, working with him, we have one of the most loyal groups of people with whom I have ever been associated. I think that all of us, whenever we get a chance, should express our appreciation of the work of these individuals.

HENRY B. MULHOLLAND, M.D.

Report of the Secretary

I desire to present to the membership a brief, graphic, statistical report on the growth and development of the American Diabetes Association for the past six years. The following summaries, I trust, will give you a picture of the Association as of 1955 compared with 1949.

Number of paid employees

June 1, 1949	6
May 1, 1955	18

Plus

1955—6 employees on part-time, contract basis

Number of Committees

June 1, 1949	16
May 1, 1955	22

Plus

Editorial Board, DIABETES
Editorial Advisory Board, ADA FORECAST
Board of Governors

Geographical location of offices

1949	
General Administration	Brooklyn, N. Y. Washington, D. C.
ADA FORECAST Office	Philadelphia, Pa.
Diabetes Detection Drive Office	Boston, Mass.
1955	
All Offices	New York, N. Y.

Income and expenses

	Income	Expenses
1949	$ 48,024.00	$ 49,130.05
1955	210,033.00	206,311.00

County and state committees on diabetes

1949	67
1955	905

Public education and case finding

	Budget
1949	$ 8,000.00
1955	43,550.00

Affiliate Associations
June 1, 1949—20
June 1, 1955—38

Subscriptions to DIABETES, *The Journal of the American Diabetes Association*

January 1952	1,622
May 1955	2,974

Subscriptions to the ADA FORECAST

June 1, 1949		8,000
May 1, 1955		
United States	29,077	
Canada	2,275	
		31,352

Membership

May 1949		
Active members	1,180	
Associate members	34	
Corporate members	25	
Total		1,239
May 1955		
Active members	2,027	
Associate members	47	
Corporate members	26	
Total		2,100

I should like to call to your attention several points in the foregoing summations. In 1949 we had offices in four different geographical locations. It was deemed advisable by the Council to consolidate these offices into one national headquarters, which was rapidly done, and our New York office is now the central site of our activities. The Council considered a number of cities for the central office. The selection of New York City has proved to be, I believe, most satisfactory.

The growth of the work of the Association has necessitated an increase in the number of employees in the central office as indicated in the first table. The six part-time employees are used on various occasions, especially during Diabetes Week, and when the work load is heavy.

Public Education and Case Finding is our greatest service program and has literally mushroomed in growth as indicated, not only by the Budget, but also by the interest shown through the growth of County and State Committees on Diabetes.

In 1952 the Association launched its scientific Journal, DIABETES. Its acceptance has been good and is evidenced by the rapid subscription growth. The increase in subscriptions to ADA FORECAST has been phenomenal and it is pleasing to announce that this magazine is self-sustaining financially.

Like all national medical associations we have more or less constant problems. Operating problems are competently and readily solved by Council deliberation and by National Office performance. We are indeed fortunate in having an excellent group of workers in the National Office under the leadership of Mr. J. Richard Connelly, our Executive Director. Three major problems probably confront us and are gradually reaching solution. One is our financial program which is now being carefully reviewed. Soon a fund-raising program of a sound, dignified type will be launched. This involves our Affiliate organization structure and with the recent establishment of the Board of Governors, and the Assembly of Delegates these problems will, we hope, ultimately reach sound adjustment. A delineation of our

future program policies is being studied in reference to our present four-fold purposes which will serve as a guide for future activities.

It is my opinion that the Officers, the Council, and the numerous Committees of the American Diabetes Association have presented a broad educational program to physicians, to diabetics, and to the public. All this work has been made possible through the splendid cooperation of the entire membership of the Association.

JOHN A. REED, M.D.

Report of the Executive Director

This isn't a report and there is no pretext of making one. Time is short and this is the place for the Officers to give their official reports.

During the year I talk or correspond with many of you, but unfortunately not with everyone. I always think that I will have an opportunity to do so at the Annual Meeting; however, there never seems to be enough time, so I am using this opportunity to greet all of you.

Although the Association has embarked on many programs and projects, we have not lost sight of the fact that the American Diabetes Association is a membership organization. Policy-wise the Officers and Councilors can attest to this. For myself and the staff I wish also to assure you that we never lose sight of the fact that the Association is composed of 2,100 individuals.

There are many of you with whom I promised to talk and in some instances, because of the over-all schedule, we are sometimes unable to complete our conversations. I will be in the back of the room or in the outer hall all afternoon and I will be delighted to see anyone at any time.

If any of you are ever in New York—and for those in the area too—I hope that you will not hesitate to drop by the office to see the headquarters and visit with us. Thank you.

J. RICHARD CONNELLY

Report of the Nominating Committee

We call your attention to the fact that there is a provision in the Constitution and Bylaws which states that individuals shall not serve as elected Councilors for more than two consecutive terms, that is, two three-year terms or a total of six years. Accordingly, it is with regret that we announce the retirement from the Council of Dr. George E. Anderson, of Brooklyn, and Dr. A. Lawrence Chute, of Toronto.

We recommend that the two vacancies created by the retirement of Drs. Anderson and Chute be filled by: Dr. John E. Howard, of Baltimore, and Dr. Robert H. Williams, of Seattle, for the three-year term which expires in 1958.

The other four members of the group of Councilors whose terms expire this year are eligible for re-election, and we recommend that they be elected for the term expiring in 1958. They are: Dr. Joseph T. Beardwood, Jr., of Philadelphia; Dr. Alexander Marble, of Boston; Dr. Thomas P. Sharkey, of Dayton; and Dr. John H. Warvel, of Indianapolis.

Our nominations for Officers of the Association for the ensuing year are as follows:

For President: Dr. Henry T. Ricketts, of Chicago; for First Vice President, Dr. Frederick W. Williams, of New York; for Second Vice President, Dr. John A. Reed, of Washington; for Secretary, Dr. Franklin B. Peck, Sr., of Indianapolis; and, for Treasurer, Dr. William H. Olmsted, of St. Louis.

(It was moved, seconded and voted that the nominations be closed. The nominees included in the report of the Nominating Committee were duly elected.)

Since the election of Dr. Peck to the Secretaryship of the Association leaves one vacancy in the Council, we nominate Dr. Charles H. Best of Toronto, to fill his unexpired term expiring in the class of 1957.

(It was moved, seconded and voted that the nominations be closed. Dr. Best was duly elected.)

ARTHUR R. COLWELL, M.D., *Chairman*
FRANK N. ALLAN, M.D.
RANDALL G. SPRAGUE, M.D.

RESEARCH GRANT AVAILABLE

The Council of the American Diabetes Association has accepted the sum of $7,500 from the Atlas Powder Company, as reported in previous issues of DIABETES. These funds are to be awarded to individual(s) for research on the metabolism of sorbitol in the human diabetic. The outline of research, including personnel and physical facilities, should be submitted to the Chairman of the Committee on Research and Fellowships at the National Office of the Association. This Committee will select the recipient(s) of the grant.

ADA RESEARCH FELLOWSHIPS FOR ACADEMIC YEAR 1956-57

The deadline for the submission of applications for Research Fellowships for 1956-57 is Nov. 15, 1955. Inquiries pertaining to them should be addressed to the National Office. Announcement of two recently awarded Fellowships appeared in the May-June issue of DIABETES.

SIXTEENTH ANNUAL MEETING

The American Diabetes Association will hold its Sixteenth Annual Meeting in Chicago June 9-10, 1956, prior to the Annual Session of the American Medical Association, June 11-15. The Drake hotel will serve as headquarters.

Scientific Program. Physicians and other scientists are invited by John A. Reed, M.D., Chairman of the Committee on Scientific Programs, to submit abstracts of papers which they would like to present at the Scientific Sessions.

Persons interested are requested to submit ten copies of the abstracts to facilitate review of the material by the Committee. Since a great number of abstracts will be at hand for the Committee to consider, they should be submitted early.

FOURTH POSTGRADUATE COURSE

The Fourth Postgraduate Course in Diabetes and Basic Metabolic Problems will be conducted by the American Diabetes Association at The Statler Hilton hotel in Dallas, Texas, Jan. 25-27, 1956. Director of the Course is Edwin L. Rippy, M.D., of Dallas, an Association Councilor and Chairman of the Committee on Policies.

Clinical diabetes and complications of diabetes will be the main topics of the Course. While details are subject to change, these features are being planned:

On January 26, a series of five different lectures and clinics for a period of one hour will be held. Registrants may designate which discussion they wish to attend. At the conclusion of the Session on January 27, five informal seminars will be conducted, each presided over by a chairman.

Round table luncheons on each of the three days, one of which will feature a panel discussion, will be presided over by a chairman. A social hour and dinner will be held January 25, and a social hour is also scheduled for January 26. On January 27 at 8 p.m., a Lay Society Meeting will be held by the Dallas Diabetes Association.

Those who plan to attend the Course are urged to register as soon as possible. All inquiries and applications should be addressed to the National Office of the ADA.

Free Admission for Medical Students and Others. The Council of the ADA accepted, at its meeting June 3-4 in Atlantic City, the following recommendation of the Committee on Professional Education regarding the admission of graduate students, fellows, residents, interns and medical students to Postgraduate Courses:

"It is recommended that such individuals on a full-time study in medicine and allied sciences in the schools and hospitals of the area, be admitted without charge to the scientific sessions upon presentation of a letter requesting their admission from their Dean, or the head of their department or service."

CHANGE IN COMMITTEE NAME

The name of the Committee on Therapeutics has been changed to the Committee on Therapeutic Agents and Devices. The change was made by the Council upon the recommendation of the Executive Committee at the Annual Meeting in Atlantic City, New Jersey, June 3-4.

NEW SUBSCRIPTION RATES FOR MEDICAL STUDENTS, INTERNS, RESIDENTS

Medical students, interns and residents are again reminded that they may now subscribe to DIABETES at the special price of $4.50 a year, half of the regular subscription rate. This reduction was accepted by the Council upon recommendation of the Committee on Scientific Publications.

NEW MEMBERS

The following Active Members were elected as of July 1, 1955:

Connecticut
Lockward, Howard J. — Manchester

Indiana
Tomlin, Hugh M. — Muncie

Maryland
Field, James B. — Bethesda

Minnesota
Nelson, W. O. B. — Fergus Falls

New York
Kramer, Louis B. — Niagara Falls
Sapsin, William — Canton

North Carolina
Warshauer, Samuel E. — Wilmington

Ohio
Bianco, Michael C. — Akron
Yochem, Donald E. — Columbus

Pennsylvania
Kleinguenther, C. J. — Philadelphia

OTHER COUNTRIES

Argentina
Landa, Jose A. — Buenos Aires

Chile
Valiente, Sergio J. — Santiago

Uruguay
Temesio, Peria M. — Montevideo

News Notes

MEETING OF THE AMERICAN MEDICAL ASSOCIATION

The 104th Annual Meeting of the American Medical Association was held from June 6-10, 1955, at Atlantic City, New Jersey. Among those participating were the following:

DWIGHT L. WILBUR, M.D., Clinical Professor of Medicine, Stanford University School of Medicine, San Francisco, was moderator at Monday's Scientific Meeting on "Diseases of the Upper Abdomen."

N. C. HIGHTOWER, M.D., Temple, Texas, opened Tuesday's discussion on "Esophagitis, Hiatal Hernia, and Cardiospasm—Surgical Considerations" at the Gastroenterology and Proctology Section.

THOMAS H. MCGAVACK, M.D., New York, participated in the "Panel Conference and Symposium on Current Trends and Developments in Therapy, as They Apply to General Practice" at the Tuesday Section on General Practice.

EDWARD H. RYNEARSON, M.D., Rochester, Minnesota, co-authored "The Clinical Aspects of Hyperinsulinism," presented at Friday's Section on Internal Medicine; discussion of this subject was opened by FRANCIS D. W. LUKENS, M.D., Philadelphia.

THOMAS F. FRAWLEY, M.D., Albany, co-authored "A New Therapeutic Agent in Adult and Juvenile Myxedema; Di-Triiodothyronine (DI-TIT)," discussion of which was opened by DR. MCGAVACK.

BERNARD BECKER, M.D., St. Louis, Missouri, discussed "The Treatment of Glaucoma with Chronic Administration of Diamox," at the Thursday Section on Ophthalmology. DR. BECKER also spoke on "The Effect of Diamox upon the Composition of the Rabbit Aqueous Humor," at the Symposium on Recent Trends in Diamox Research at Wednesday's Section on Research in Ophthalmology.

At the same meeting JONAS FRIEDENWALD, M.D., Baltimore, discussed "Further Studies on Diamox and Aqueous Flow."

DAVID ADLERSBERG, M.D., New York, discussed "Inborn Errors of Lipid Metabolism: Clinical, Genetic, and Chemical Aspects" at the Tuesday Section on Pathology and Physiology, discussion of which was opened by S. J. THANNHAUSER, M.D., Boston.

B. J. KENNEDY, M.D., Minneapolis, opened the discussion on "The Management of Metastatic Mammary Cancer" at Tuesday's Section on Surgery.

SALVATORE R. LA TONA, M.D., University of Buffalo School of Medicine, Buffalo, was co-sponsor of a scientific exhibit on Arthritis and Rheumatism. The title of the exhibit was "Is it Osteoarthritis?"

The exhibit symposium on diabetes was arranged by HOWARD F. ROOT, M.D., Boston, with the assistance of members of the American Diabetes Association. The exhibit of the American Diabetes Association was presented by WILLIAM R. KIRTLEY, M.D., Chairman of the Committee on Scientific Exhibits; DR. HENRY B. MULHOLLAND, President, and other members of the Association. JAMES M. MOSS, M.D., and DEWITT E. DE LAWTER, M.D., Georgetown University School of Medicine, Washington, D. C., co-sponsored the exhibit titled "Today's Great Imitator, Diabetes Mellitus." HUGH L. C. WILKERSON, M.D., Boston, U. S. Department of Health, Education, and Welfare, Public Health Service, co-sponsored with ARNOLD B. KURLANDER, M.D., Washington, D. C., the exhibit on "Diabetes: Blood Sugar Screening in the Physician's Office."

The exhibit on "Diabetes Today" was arranged by DR. ROOT, ELLIOTT P. JOSLIN, M.D., PRISCILLA WHITE, M.D., ALEXANDER MARBLE, M.D., ALLEN P. JOSLIN, M.D., ROBERT F. BRADLEY, M.D., and LEO P. KRALL, M.D., Joslin Clinic, Boston.

The Diabetes Conferences were opened on Monday by DR. ROOT, with a question and answer period titled "Diabetic Acidosis." The Conferences also included "Children of Diabetic Mothers," by DR. WHITE; "Office Treatment," by FRANK N. ALLAN, M.D., Boston; "Treatment of Brittle Diabetes," by DR. MARBLE; "Glucagon and Insulin," by GEORGE E. ANDERSON, M.D., Brooklyn, N. Y. A panel on "What Is the Nature of Diabetes?" was held by DRS. ANDERSON, WHITE, MARBLE, ROOT, and CHARLES W. STYRON, M.D., Raleigh.

Tuesday's Conferences included: "Juvenile Diabetes Today and Tomorrow," by Dr. WHITE; "Maintenance of Body Base Stores," by NANCY NICHOLS, M.D., Boston; "Triopathy of Diabetes and its Control," by DR. ROOT; "Electrolytes in Ketosis," by GEORGE NICHOLS, M.D., Boston; "Penalties of Delay in Diagnosis and Treatment," by DR. STYRON; and a panel discussion on "Problems in Diabetic Pregnancy and the Influence of Heredity," by DRS. MULHOLLAND, WHITE, WILKERSON, and ROOT.

Wednesday's Conference included "Diabetes in Old Age," by DR. ROOT; "Action of Different Types of Depot Insulin," by ARTHUR R. COLWELL, M.D.; "Symptoms and Diagnosis," by JAMES M. MOSS, M.D., Washington, D. C.; "Diet in Treatment of Early and Late Cases," by DR. BRADLEY; "Use of Insulin Combina-

tions," by DR. KRALL; and a panel discussion on "Diet and Insulin in the Treatment of Diabetes and Its Complications," by DRS. ELLIOTT P. JOSLIN, BRADLEY, KRALL, and MOSS.

Thursday's Conference included "Diabetes Today," by DR. ELLIOTT P. JOSLIN; "Treatment in Youth," by GEORGE F. SCHMITT, M.D., Miami, Florida; "Screening for Diabetes," by DR. WILKERSON; "Aids in Management of Coma," by DR. KRALL; "Hepatic and Other Factors in Hypoglycemia," by DR. BRADLEY; and a panel discussion on the "Management of Diabetic Emergencies," by DRS. KIRTLEY, KRALL, LUKENS, and SCHMITT.

DAVID ADLERSBERG, M.D., co-sponsored "The Effect of Heparin on Plasma Lipids in Abnormal States of Lipid Metabolism" in the Scientific Exhibit of Experimental Medicine. LAURANCE W. KINSELL, M.D., Oakland, California, co-sponsored an exhibit "Prednisone and Prednisolone: Comparative, Clinical and Metabolic Evaluation" in the same section.

R. G. SPRAGUE, M.D., Rochester, Minnesota, co-sponsored a scientific exhibit on "Cushing's Syndrome" at the Internal Medicine Section. In the same section ROBERT W. SCHNEIDER, M.D., Cleveland Clinic, Cleveland, co-sponsored an exhibit on "Primary Hyperparathyroidism—A Curable Disease."

W. EARL REDFERN, M.D., Henry Ford Hospital, Detroit, co-sponsored a scientific exhibit on "Hypoglycemia and Hyperinsulinism" at the Section on General Practice. At the same section DR. SCHMITT prepared an exhibit on "Drug Therapy of Hypertension."

An exhibit on "Mental Disorders in the United States: Some Indications of the Size and Scope of the Problem" was co-sponsored by HERBERT H. MARKS, Metropolitan Life Insurance Company, New York. This was in the section on Nervous and Mental Diseases.

ALVAH L. NEWCOMB, M.D., Evanston Hospital, Evanston, Illinois, prepared an exhibit on "The Breast Milk Bank As a Community Project," in the Section on Pediatrics.

NIH MEDICAL RESEARCH GRANTS

The National Institutes of Health in May disclosed approval of 742 research grants for which $8,418,135 has been allocated. New projects number 280, and continuations, 462. The list includes 104 grants for arthritis and metabolic diseases, $988, 392; 82 for neurological diseases and blindness, $637,794; 155 for cancer, $1,934,540; eight for dental problems, $90,652; 63 for microbiology, $532,949; 183 for heart disease, $2,194,479; 63 grants for mental disorders, $1,127,839. Also, 84 grants, totaling $911,490, have been made, embracing nonclassified medical research.

In July Congress increased grants to component institutes of NIH when it approved the appropriations bill for 1955-56 of the Department of Health, Education, and Welfare, earmarked as follows:

Cancer chemotherapy, $2,000,000; demonstrations in early diagnosis of cervical cancer, $500,000; virus research, chiefly in upper respiratory diseases, $185,000; expansion of biologics control, stressing poliomyelitis vaccine studies, $750,000; arthritis and metabolic diseases, $2,000,000; training and research in neurological and sensory disorders, $1,000,000; heart research and training $1,500,000.

In addition to this, $500,000 above the budgetary request submitted by the Administration was appropriated for support of noncategorical research.

POSTGRADUATE MEDICAL CRUISE

"Etiology and Clinical Course of Diabetes Mellitus," and "Treatment of Diabetes Mellitus and Its Complications," are among the subjects included in the proposed program of the 12-day Postgraduate Medical Cruise sponsored by Duke University School of Medicine.

The course will be held aboard the new transatlantic liner M.S. "Stockholm," which will sail to the Caribbean from Wilmington, North Carolina, Nov. 23, 1955.

William M. Nicholson, M.D., Professor of Medicine and Director of Postgraduate Education at Duke University, is on the faculty of the course.

PERSONALS

CHARLES H. BEST, M.D., Professor of Physiology at the University of Toronto, was one of fourteen persons whose appointments to the Pontifical Academy of Science were announced recently by Pope Pius XII. The Pontifical Academy of Science, founded in 1603, is composed of seventy academicians. With the most recent additions it numbers sixty-six members.

EDWARD L. BORTZ, M.D., served as alternate for the Medical Society of the State of Pennsylvania to the House of Delegates at the American Medical Association Annual Meeting held in June at Atlantic City.

JØRN DITZEL, M.D., has become Associate in Clinical Research at the Baker Clinic Research Laboratory, New England Deaconess Hospital and the Joslin Clinic, Boston.

FRANK L. ENGEL, M.D., Associate Professor of Medi-

cine, Duke University, will be chairman of Tuesday's meeting of the Seventh Annual Postgraduate Assembly in Endocrinology and Metabolism of the Endocrine Society, given in cooperation with the Indiana University School of Medicine, at Indiana University Medical Center, Indianapolis, Indiana, Sept. 26-Oct. 1, 1955. He will speak on "Examination of the Patient for Endocrine Disease," "Hyperparathyroidism," "Adrenal Insufficiency," and "Use of Cortisone, Corticotropin, and Related Substances—Management of Patient before and after Adrenal Surgery."

GLENN W. IRWIN, M.D., Assistant Professor of Medicine, Indiana University School of Medicine, will speak on "Hypoparathyroidism," and "Adrenal Medulla-Pheochromocytoma."

EDWARD H. RYNEARSON, M.D., Chairman of Sections on Endocrinology and Metabolism, Rochester, Minnesota, will speak on "Hyperinsulinism and Spontaneous Hypoglycemia" and "Obesity and Leanness."

DON E. WOOD, M.D., Associate Professor of Medicine, Indiana University School of Medicine, is Chairman of the Local Committee on Arrangements, and Chairman of the Monday Session. He will speak on "Demonstration of Laboratory Procedures," "Gynecomastia—Klinefelter's Syndrome," "Case Presentations—Pituitary, Thyroid, Parathyroids, Adrenals, Testes," and participate in the questions and answers at Friday's "Case Presentation—Ovaries."

FRANKLIN B. PECK, SR., M.D., will speak on "Chemistry and Actions of Available Insulins," and "Pointers in Management of Complications of Diabetes" October 1. CHARLES E. TEST, M.D., will present "Essentials in Management of Uncomplicated Diabetes" on the same day.

DWIGHT J. INGLE, PH.D., and FRANCIS D. W. LUKENS, M.D., are members of the Council of the Endocrine Society. DRS. LUKENS, ENGEL, and C. N. H. LONG, M.D., are members of the Postgraduate Committee.

IRVING GRAEF, M.D., Fourth Medical Division (New York University) Bellevue Hospital, New York, received a grant of $4,000 on July 1, 1955, from The National Vitamin Foundation, Inc., for studies of the effect of pantothenic acid deficiency in various disease states.

JOSEPH P. HOET, M.D., Professor of Medicine, University of Louvain, Belgium, spoke on various aspects of pregnancy in diabetes at a series of meetings held in March and April in Detroit, New York, and Boston. His lecture at the Ninth Annual Meeting of the Michigan Clinical Institute was sponsored by the Michigan Diabetes Association, the Michigan Society of Obstetricians and Gynecologists, and the Detroit Pediatric Society, with RICHARD M. MCKEAN, M.D., LAURENCE F. SEGAR, M.D., HAROLD A. OTT, M.D., and MANES S. HECHT, M.D., all of Detroit, as the Committee on Arrangements. DR. HOET also lectured at the New York Academy of Medicine, Columbia University, the Merck Institute of Medical Research, Bellevue Hospital, Jewish Chronic Disease Hospital of Brooklyn, and the Joslin Clinic.

HENRY B. MULHOLLAND, M.D., was reelected to the Council on Medical Service of the American Medical Association at its Annual Meeting in Atlantic City held in June. Dr. Mulholland has been serving as Vice Chairman of the Council.

MICHAEL G. WOHL, M.D., spoke on "The Relation of Cholesterol Metabolism to Coronary Artery Disease and Nutritional and Metabolic Aspects of Cardiac Failure" at a meeting of the Ninth Community Nutrition Institute on June 22, 1955, at Syracuse, New York. The meeting was sponsored by Syracuse University and the New York State Department of Public Health.

OBITUARY

JAMES W. CALLAWAY, M.D., was born in Temple, Texas, in 1907, and died in La Jolla, California, on June 25, 1954. He received his medical degree from Northwestern University Medical School in 1932, interned at St. Luke's Hospital in Chicago, and was resident at Municipal Contagious Diseases Hospital in Chicago. From 1934 to 1954, he was Associate of the Scripps Metabolic Clinic in La Jolla, California, and a Staff Member of the Scripps Memorial Hospital. He became a member of the American Diabetes Association in 1948. He was also a Fellow of the American College of Physicians, and a Diplomate of the American Board of Internal Medicine. Dr. Callaway was a Civilian Medical Consultant at Camp Pendleton Navy Hospital, Camp Pendleton, California. Entering the United States Army in 1940 as a Captain in the Medical Corps, he rose to Lieutenant Colonel before being separated from the service in 1945. His specialty was Internal Medicine, and diseases of metabolism.

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